

**Synthesis of an  $\alpha$ ,3-Dehydrotoluene Biradical Precursor with DNA  
Cleaving Activity and Studies Directed Toward the Total Synthesis of  
Tetracycline**

Thesis by  
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*In memory of my loving grandparents...  
Somehow, I know you are cheering for me right now.*

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## Abstract

The synthesis and characterization of a model of the enediyne antibiotics is described. The prepared conjugate consists of an  $\alpha,3$ -dehydrotoluene biradical precursor tethered to an *N*-methylpyrrolicarboxamide minor groove binding element. The conjugate is shown to bind and cleave DNA with sequence selectivity. The binding domain is shown to localize the allene-ene-yne effector domain for sequence-selective DNA cleavage at micromolar concentrations of substrate. The time course of DNA cleavage parallels the rate of cyclization of the bioconjugate in organic solvent to form an  $\alpha,3$ -dehydrotoluene biradical. These results indicate that the (*Z*)-allene-ene-yne functional group is a viable effector domain for the cleavage of DNA upon mild thermal activation.

Synthetic studies directed toward a concise and versatile synthesis of the antibiotic tetracycline are described. A strategy based on an isobenzofuran Diels–Alder cycloaddition to assemble the two halves of tetracycline is presented. The synthesis of the phthalide left-hand half is shown in five steps with 56% overall yield from commercially available starting materials. Several isobenzofuran Diels–Alder reactions are described that model the proposed condensation of the two halves of tetracycline. Specifically, a thermal Diels–Alder reaction is successfully demonstrated with an enone dienophile containing an  $\alpha$ -ester functional group. The synthesis of 6-dimethylaminomethyl-2,2-dimethyl-1,3-dioxin-4-one as a protected and fully functionalized right-hand half of the A ring of tetracycline is described. Strategies are discussed that aim to utilize this substrate in the synthesis of the right-hand half of tetracycline. A novel and potentially rapid route involving intermediate 2,4- or 2,5-cyclohexadienones from the oxidation of phenol precursors is briefly examined.

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**List of Abbreviations**

|                  |                                    |
|------------------|------------------------------------|
| A                | adenine                            |
| Å                | angstrom                           |
| Ac               | acetyl                             |
| AIBN             | 2,2'-azobis(isobutyronitrile)      |
| APT              | attached proton test               |
| bp               | base pair(s)                       |
| Bu               | butyl                              |
| C                | cytosine                           |
| °C               | degrees Celsius                    |
| cat.             | catalytic                          |
| CDI              | 1,1'-carbonyldiimidazole           |
| CHD              | 1,4-cyclohexadiene                 |
| CI               | chemical ionization                |
| cm <sup>-1</sup> | reciprocal centimeters             |
| cpm              | counts per minute                  |
| δ                | chemical shift (parts per million) |
| DABCO            | 1,4-diazabicyclo[2.2.2]octane      |
| dec              | decomposition                      |
| DIPEA            | diisopropylethylamine              |
| DIPT             | diisopropyl tartrate               |
| DMAP             | 4-dimethylaminopyridine            |
| DCE              | dichloroethane                     |
| DMDO             | dimethyldioxirane                  |
| DME              | dimethoxyethane                    |

|          |  |
|----------|--|
| DMF      | <i>N,N</i> -dimethylformamide                                  |
| DMSO     | dimethyl sulfoxide   |
| DNA      | deoxyribonucleic acid  |
| EDC      | 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide<br>hydrochloride |
| ee       | enantiomeric excess  |
| EI       | electron impact  |
| eq       | equation   |
| equiv    | equivalent(s)  |
| Et       | ethyl  |
| EtOAc    | ethyl acetate  |
| EWG      | electron-withdrawing group                                     |
| FAB      | fast atom bombardment  |
| FT       | Fourier transform  |
| g        | gram   |
| G        | guanine  |
| h        | hour   |
| HMDS     | hexamethyldisilazane   |
| HPLC     | high performance liquid chromatography                         |
| HRMS     | high resolution mass spectroscopy                              |
| Hz       | hertz  |
| <i>i</i> | iso  |
| IR       | infrared   |
| <i>J</i> | coupling constant  |
| k        | rate constant  |
| KHMDS    | potassium bis(trimethylsilyl)amide                             |
| KOt-Bu   | potassium <i>tert</i> -butoxide                                |

|                  |   |
|------------------|---|
| L                | liter   |
| LDA              | lithium diisopropylamide                        |
| LHMDS            | lithium bis(trimethylsilyl)amide                |
| <i>m</i>         | <i>meta</i>                                     |
| M                | Molar   |
| [M] <sup>+</sup> | molecular ion                                   |
| <i>m</i> -CPBA   | <i>meta</i> -chloroperoxybenzoic acid           |
| mg               | milligram                                       |
| MHz              | megahertz                                       |
| min              | minute(s)                                       |
| mL               | milliliter                                      |
| mM               | millimolar                                      |
| mmol             | millimole                                       |
| mol              | mole  |
| mp               | melting point                                   |
| MPE              | methidiumpropyl-ethylenediaminetetraacetic acid |
| MTAD             | 4-methyl-1,2,4-triazoline-3,5-dione             |
| μL               | microliter                                      |
| μm               | micron  |
| μM               | micromolar                                      |
| μmol             | micromole                                       |
| <i>n</i>         | normal  |
| N                | normal (concentration)                          |
| nm               | nanometer                                       |
| nM               | nanomolar                                       |
| NMR              | nuclear magnetic resonance                      |
| nOe              | nuclear Overhauser effect                       |

|           |  |
|-----------|--|
| <i>o</i>  | <i>ortho</i>                           |
| o.d.      | outer diameter                         |
| <i>p</i>  | <i>para</i>                            |
| pH        | hydrogen ion concentration (log scale) |
| Ph        | phenyl                                 |
| Pr        | propyl                                 |
| psi       | pounds per square inch                 |
| <i>R</i>  | rectus                                 |
| $R_f$     | retention factor                       |
| rp        | reverse-phase                          |
| s         | seconds                                |
| <i>S</i>  | sinister                               |
| SEM       | 2-(trimethylsilyl)ethoxymethyl         |
| <i>t</i>  | tertiary                               |
| T         | thymine                                |
| $t_{1/2}$ | half-life                              |
| TBAF      | tetrabutylammonium fluoride            |
| TBHP      | <i>tert</i> -butyl hydroperoxide       |
| TBS       | <i>tert</i> -butyldimethylsilyl        |
| TDS       | <i>tert</i> -butyldiphenylsilyl        |
| Tf        | trifluoromethanesulfonate              |
| TFA       | trifluoroacetic acid                   |
| TFAA      | trifluoroacetic anhydride              |
| THF       | tetrahydrofuran                        |
| TIPS      | triisopropylsilyl                      |
| TLC       | thin layer chromatography              |
| TMS       | trimethylsilyl                         |

|              |                                 |
|--------------|---------------------------------|
| Tris         | tris(hydroxymethyl)aminomethane |
| <i>p</i> -Ts | <i>para</i> -toluenesulfonyl    |
| UV           | ultraviolet                     |
| v/v          | volume-to-volume ratio          |
| w/w          | weight-to-weight ratio          |
| Z            | zusammen                        |

## **Chapter 1**

### **Synthesis of an $\alpha,3$ -Dehydrotoluene Biradical Precursor with DNA Cleaving Activity**

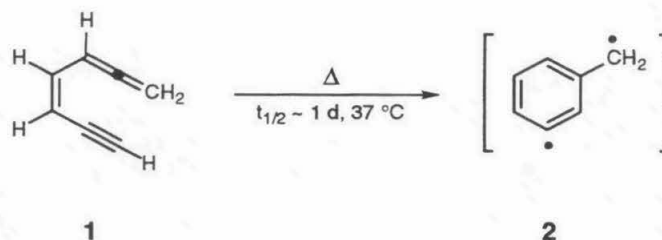
## Introduction

The naturally occurring enediyne antitumor antibiotics are a structurally unique class of molecules possessing potent DNA cleaving ability.<sup>1</sup> Their biological activity arises from the chemical activation of a highly unsaturated precursor, which subsequently undergoes cyclization to generate a reactive biradical. This intermediate is capable of abstracting hydrogen atoms from the deoxyribose backbone of double-stranded DNA in a site-specific manner. To further characterize and understand the mode of action of the enediyne antibiotics, much effort has been directed towards the construction of model compounds capable of biradical formation and thus having the potential for DNA cleavage.<sup>2</sup>

Several novel compounds which produce 1,4-biradical intermediates upon both chemical and thermal activation have been reported from this group.<sup>3-5</sup> In an effort to establish and characterize any DNA cleaving capabilities these systems may possess, a model substrate was envisioned consisting of three distinct portions: (1) a latent biradical precursor; (2) an agent with recognized affinity for DNA to provide the biradical precursor with similar DNA binding properties; and (3) a tether to connect these two moieties. Herein is described a completely synthetic model of the enediyne antibiotics which, upon thermal activation, gives rise to an  $\alpha,3$ -dehydrotoluene biradical capable of site-selective DNA cleavage.<sup>6</sup>

## Background

The (Z)-allene-ene-yne functional group has been shown to undergo a facile unimolecular thermal isomerization reaction to form an  $\alpha,3$ -dehydroalkylbenzene biradical intermediate.<sup>3,4</sup> The cycloaromatization of (Z)-1,2,4-heptatriene-6-yne (**1**) to  $\alpha,3$ -dehydrotoluene (**2**) may be considered prototypical, occurring with a half-life of about one day at 37 °C. The  $\alpha,3$ -dehydroalkylbenzene biradicals produced in these cyclization reactions exhibit reactivity that is consistent with traditional definitions of both radical and polar (zwitterionic) species. For example, the thermal cyclization of (Z)-allene-ene-yne **3**

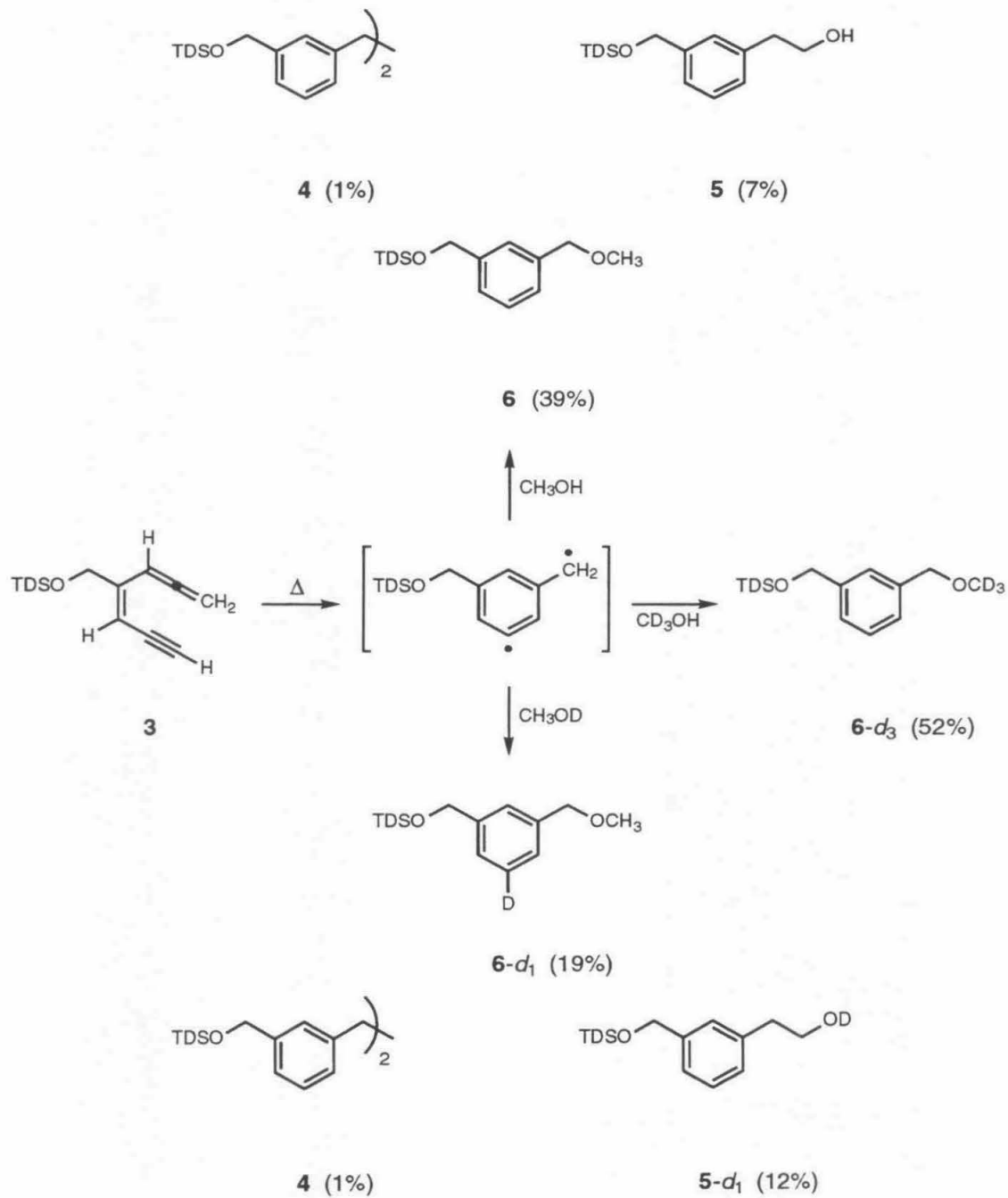


in methanol leads to the formation of products consistent with a free radical description of the biradical intermediate, the bibenzyl derivative **4** (1% yield) and the alcohol **5** (7% yield), in addition to the methyl ether **6** (39% yield), a product anticipated from a polar description of the biradical intermediate wherein the benzylic carbon is  $\delta^+$  and the *m*-aryl carbon is  $\delta^-$  (Scheme I). The distribution of polar versus free radical products varies with subtle changes in the reaction medium in an entirely predictable fashion. Substitution of deuterium for protium on the methanol carbon ( $\text{CD}_3\text{OH}$ ) leads to the exclusive formation of the product derived from a polar reaction mechanism, the (deuterated) methyl ether **6-*d*<sub>3</sub>**, while substitution of the hydroxylic proton of methanol with deuterium ( $\text{CH}_3\text{OD}$ ) skews the product distribution towards that of a free radical reaction mechanism (Scheme I).

The ability of  $\alpha,3$ -dehydroalkylbenzene biradicals to abstract a hydrogen atom from the methyl group of methanol raises the possibility that these species might function as DNA damaging agents, in analogy to the biradical intermediates arising from the enediyne antibiotics. However, the variation of the branching ratio between radical and polar reaction pathways with relatively small changes in the bond dissociation energy of the hydrogen atom donor and with the acidity of the medium<sup>4</sup> makes it difficult to predict just how an  $\alpha,3$ -dehydrotoluene intermediate might react with double-stranded DNA in an aqueous environment. It is easy to imagine that the primary reaction pathway might involve the addition of water by a polar mechanism. On the other hand, if the biradical were formed in the minor groove of DNA, then it may well react in a manner analogous to the enediyne antibiotics and abstract a hydrogen atom from the ribose backbone of DNA.<sup>1,2</sup> In a preliminary effort to explore this issue, the (*Z*)-allene-ene-yne **3** was heated at  $60^\circ \text{C}$  in 20% aqueous tetrahydrofuran. The purpose of the experiment was to see if the biradical

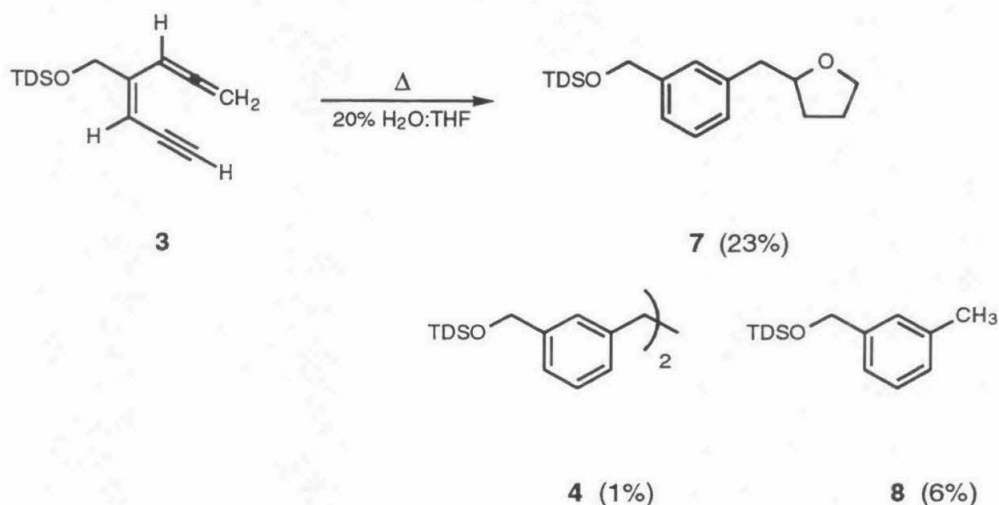


### Scheme I

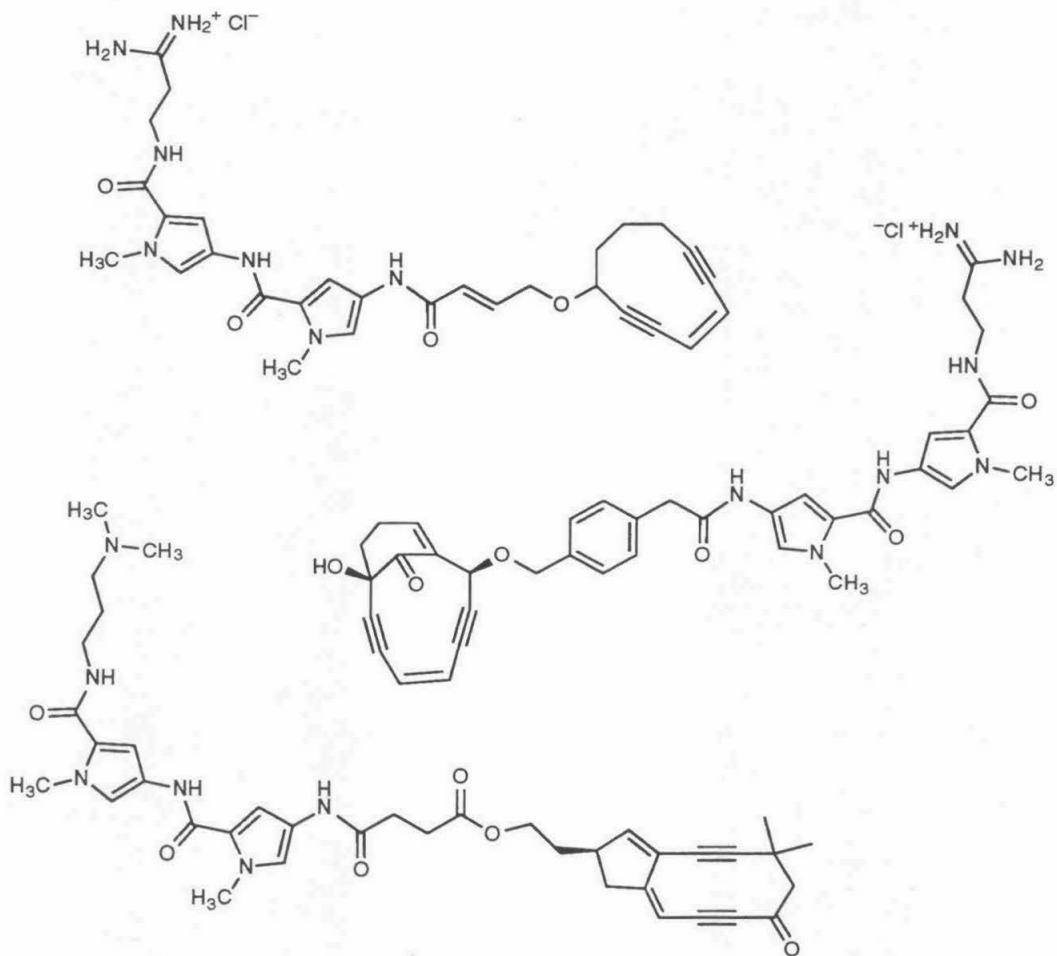


TDS = *tert*-butyldiphenylsilyl

intermediate would react preferentially with water in a polar mechanism or by hydrogen atom abstraction from the labile  $\alpha$ -CH bonds of tetrahydrofuran. In the event, only products arising from a free radical reaction mechanism (adducts **4**, **7**, and **8**) were observed. Encouraged by this result, the goal became to address in a more direct fashion the question of whether an  $\alpha$ ,3-dehydrotoluene intermediate might lead to free radical damage of double-stranded DNA.

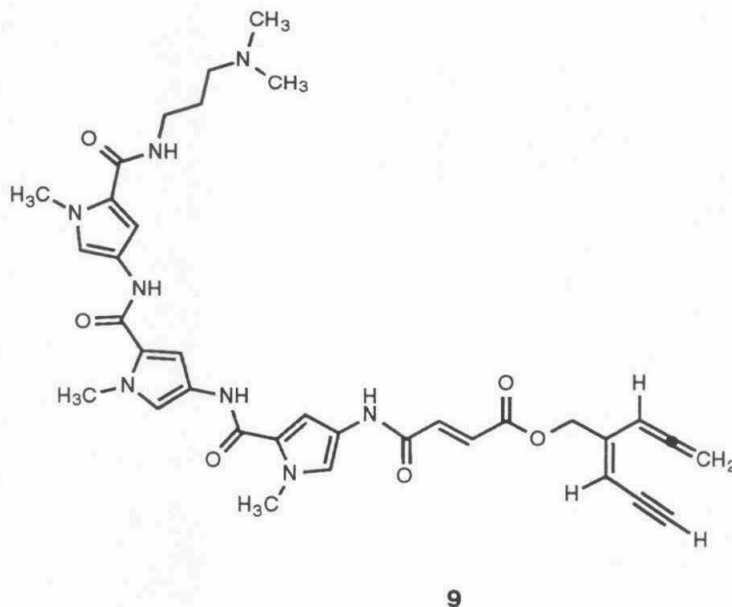


Because  $\alpha$ ,3-dehydrotoluene itself was anticipated to have a low affinity for double-stranded DNA (a speculation verified below), the well-established *N*-methylpyrrolecarboxamide DNA binding motif of the natural products distamycin and netropsin was incorporated covalently into the substrates of this work. The motif binds tightly in the minor groove of double-stranded DNA and displays high specificity for AT-rich regions of DNA.<sup>7</sup> This binding motif was first utilized by Dervan and co-workers in their development of the affinity cleavage concept and in the design of DNA-cleaving molecules.<sup>7,8</sup> It has subsequently been used for the synthesis of several bioconjugates incorporating biradical precursors (Figure 1).<sup>9-12</sup> With these substrates, it has been demonstrated that addition of the netropsin binding unit enhances cleavage ability versus control studies conducted with the model enediyne lacking a minor groove binding element. Typically, such bioconjugates have been shown to exhibit DNA cleavage in a DNA nicking



**Figure 1.** Examples of enediyne model systems linked to *N*-methylpyrrolecarboxamide binding motifs.<sup>9-11</sup>

assay, and thus the particulars of DNA binding and the site-selectivity of cleavage are generally not probed.<sup>13</sup> The synthesis of conjugate **9**, consisting of an  $\alpha,3$ -dehydrotoluene precursor covalently linked to an *N*-methylpyrrolicarboxamide minor groove binding element, and its DNA-binding and -cleaving properties are described herein.

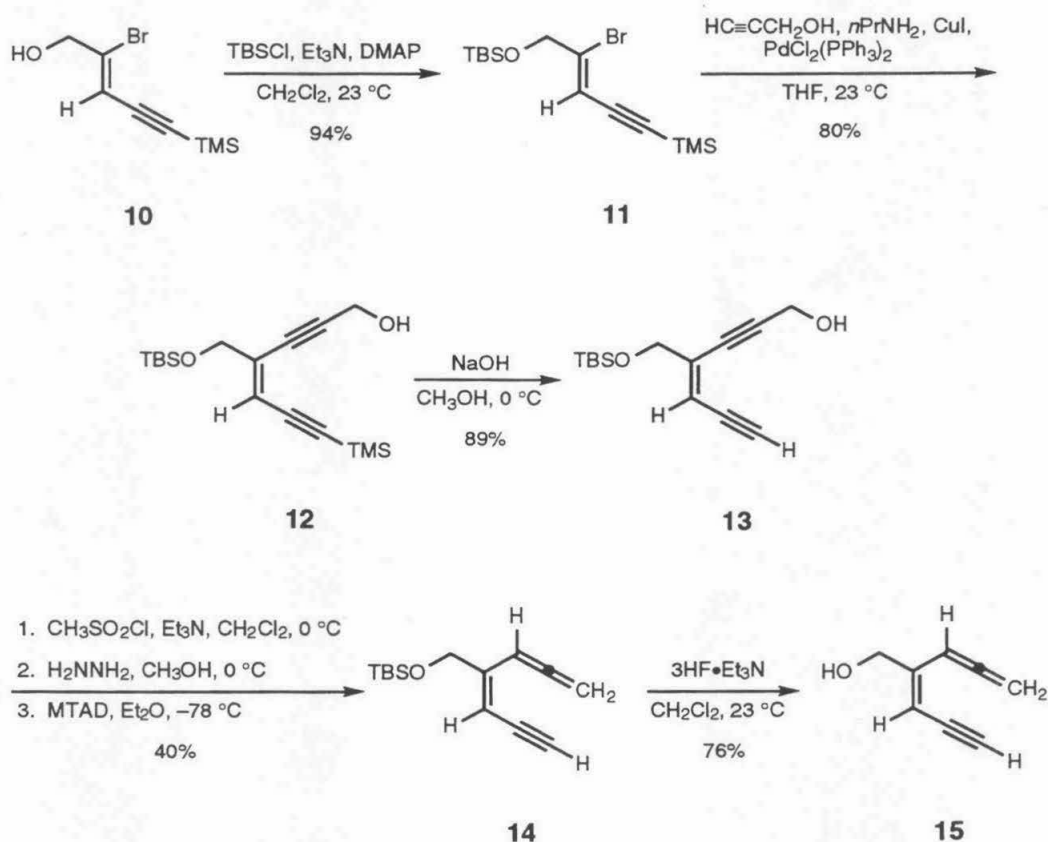


### Synthesis and Characterization of Conjugate **9**

The (Z)-allene-ene-yne alcohol **15** was prepared using methodology previously developed for the synthesis of **3** (Scheme II).<sup>4</sup> Protection of the known alcohol **10**<sup>4</sup> with *tert*-butyldimethylsilyl chloride (1.1 equiv), triethylamine (1.5 equiv), and 4-dimethylaminopyridine (0.27 equiv) in dichloromethane afforded the silyl ether **11** in 94% yield. Palladium-catalyzed coupling (cuprous iodide (0.15 equiv), bis(triphenylphosphine)palladium(II) chloride (0.05 equiv), *n*-propylamine (4.0 equiv), THF)<sup>14</sup> of **11** with propargyl alcohol (2.0 equiv) produced the (Z)-enediynes **12** (80%). Protodesilylation of the acetylenic trimethylsilyl group of **12** was accomplished in 89% yield upon addition of a sodium hydroxide solution (50% w/w) to **12** in ice-chilled methanol. The resulting alcohol **13** was transformed into the allene **14** using methodology previously developed for this purpose.<sup>15</sup> Thus, activation of the hydroxyl group of **13**

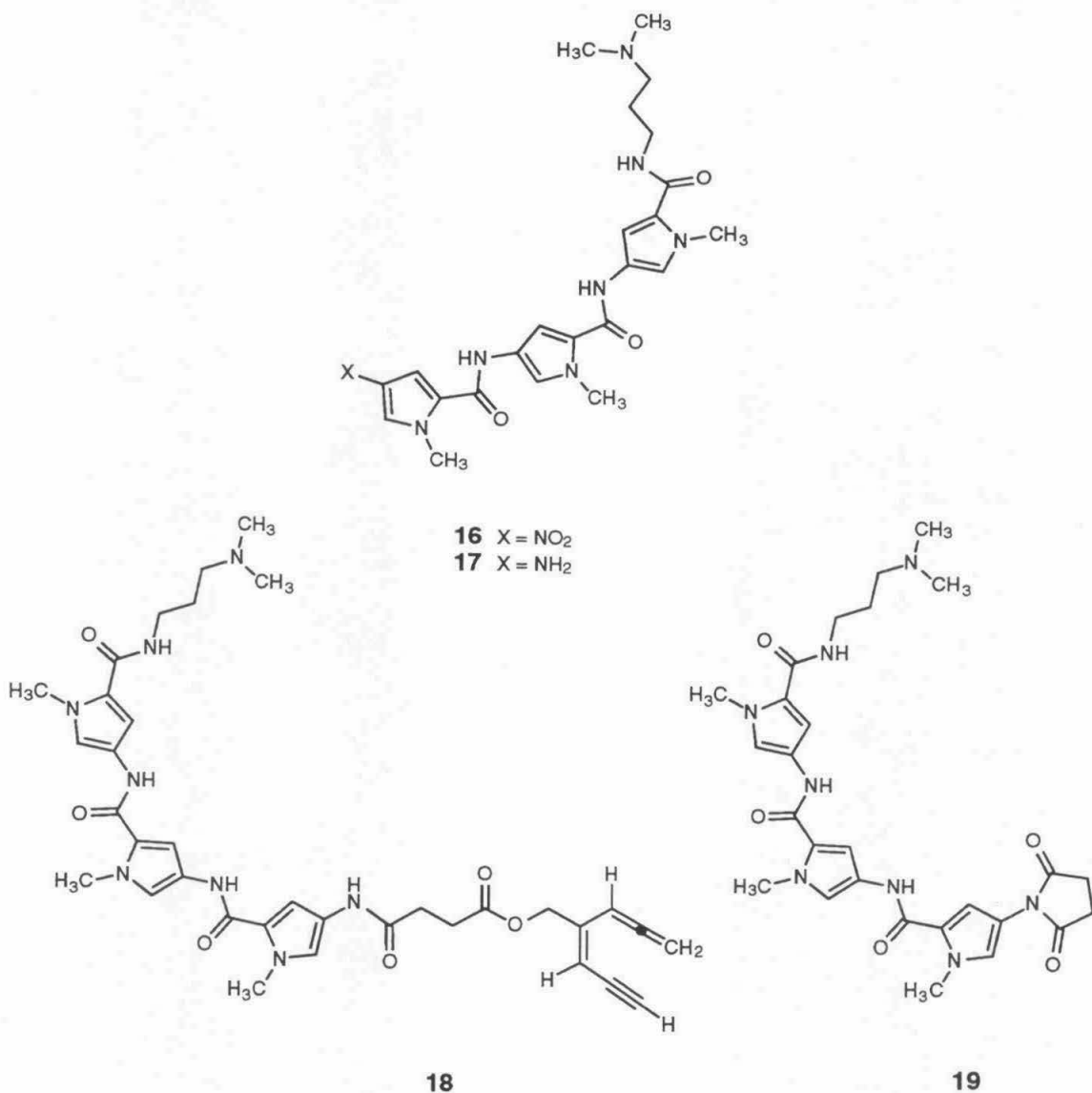
with methanesulfonyl chloride (3.0 equiv) and triethylamine (5.0 equiv) in dichloromethane (0 °C) and displacement of the resulting mesylate with hydrazine in methanol (31.8 equiv) afforded a propargylic hydrazine intermediate. Extractive isolation of this intermediate and oxidation of the crude extract with 4-methyl-1,2,4-triazoline-3,5-dione (2.0 equiv) in diethyl ether (−78 °C) produced the allene **14** in 40% yield from alcohol **13**.<sup>16</sup> Cleavage of the *tert*-butyldimethylsilyl ether group of **14** (triethylamine trihydrofluoride, CH<sub>2</sub>Cl<sub>2</sub>) then provided the biradical precursor **15** in 76% yield.

### Scheme II



The nitrodistamycin derivative **16**<sup>17</sup> is typically linked to an effector molecule via its hydrogenation product, the air-sensitive amine **17**.<sup>18</sup> Dervan and co-workers,<sup>19</sup> as well as others,<sup>10</sup> have shown that the proper choice of a linking group can be a critical component in the design of DNA-cleaving agents. Initially, a succinyl linker was chosen to couple the

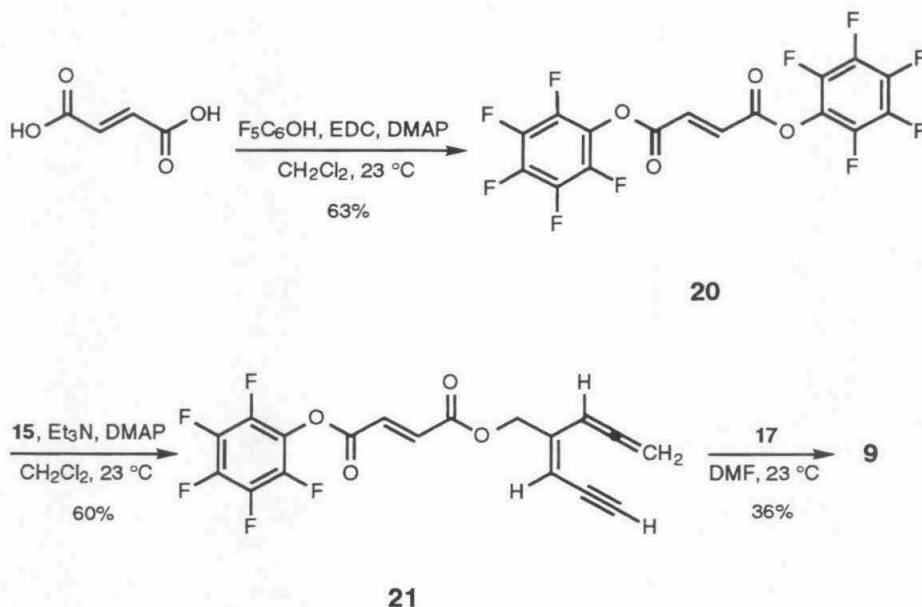
binding and effector domains, but it was found that the resulting conjugate **18** was unstable, readily cyclizing to form the imide **19** by expulsion of the alcohol **15**.



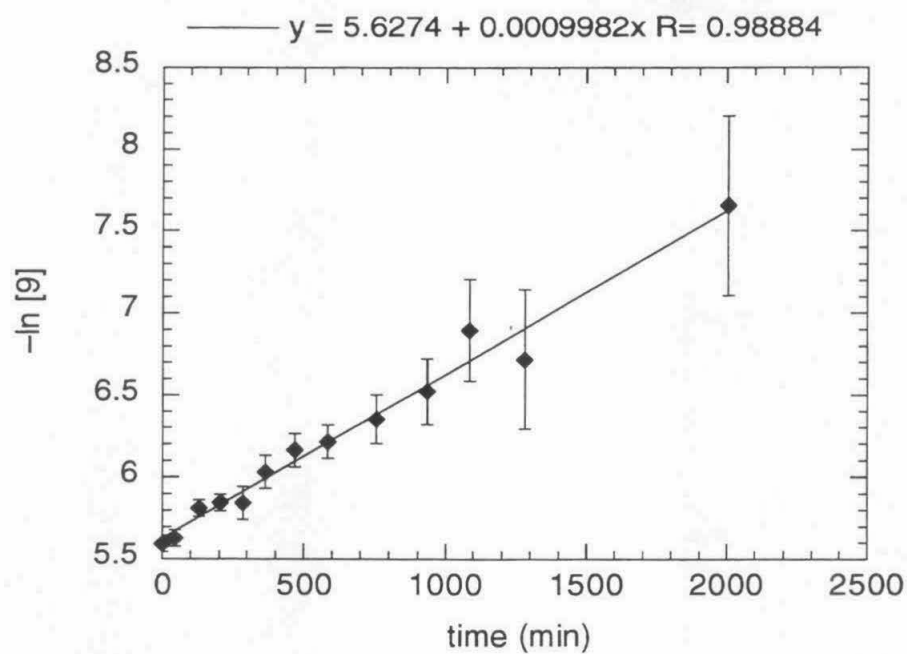
This problem was avoided by using a fumarate linking group.<sup>20</sup> Activation of fumaric acid as its bis(pentafluorophenyl) ester **20** was accomplished in 63% yield by bis-coupling with pentafluorophenol (3.0 equiv) in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.0 equiv) and DMAP (0.04 equiv) in dichloromethane (Scheme III). Addition of diester **20** (3.0 equiv) to a solution of alcohol **15** in dichloromethane containing triethylamine (5.0 equiv) and DMAP (0.01 equiv) gave rise to

the activated ester **21** (60%). When this product (1.0 equiv) was stirred with a solution of amine **17** (freshly prepared by hydrogenation<sup>17</sup> of **16** with 10% palladium on carbon in methanol) in *N,N*-dimethylformamide, the conjugate **9** was formed in 36% yield (from **16**) after purification on silica gel using 1:1 acetonitrile–methanol containing 1% concentrated ammonium hydroxide solution as the eluent.

### Scheme III



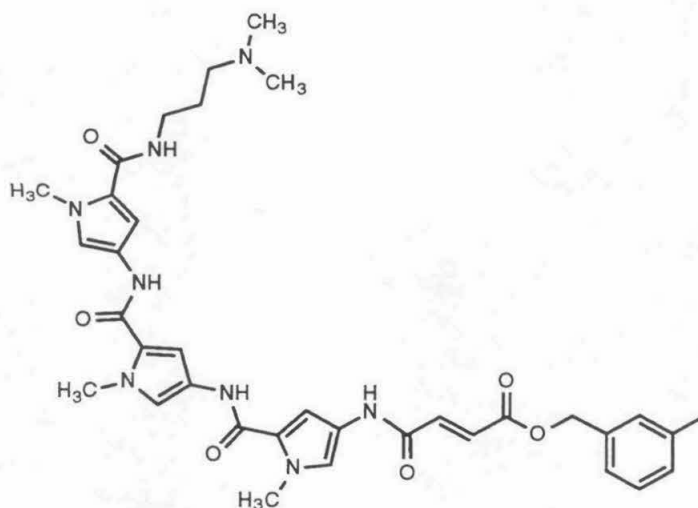
Thermal cyclizations of conjugate **9** (3.0–3.8 mM) were conducted at 37 °C in dimethyl sulfoxide-*d*<sub>6</sub> as the solvent containing 1,4-cyclohexadiene (30–300 mM) and *N,N*-dimethylformamide (25 mM, internal standard) in NMR tubes that had been sealed in vacuo. In a typical experiment, run to ~85% completion, the cyclization products **22** (25%) and **23** and **24** (inseparable mixture, 25% combined yield) were isolated by high-performance liquid chromatography (HPLC). A similar distribution of products had been observed in an earlier study of the cyclization of **3**.<sup>4</sup> The rate of cyclization of **9** at 37 °C was determined by <sup>1</sup>H NMR monitoring of the reaction as a function of time. Analysis of the data (Figure 2) established that **9** had decayed in a first-order manner with a rate constant  $k = (1.75 \pm 0.46) \times 10^{-5} \text{ s}^{-1}$  ( $t_{1/2} = 10.9 \text{ h}$ , 37 °C). This rate is somewhat faster than the rate of cyclization of **3** under similar conditions ( $8.94 \times 10^{-6} \text{ s}^{-1}$ ,  $t_{1/2} = 21.5 \text{ h}$ , 37



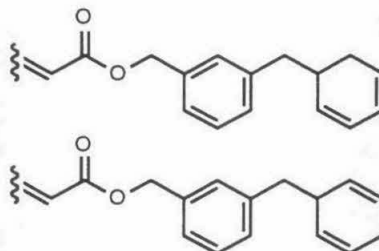
**Figure 2.** Plot of kinetic data for cyclization of **9** at 37 °C in dimethyl sulfoxide- $d_6$  containing 1,4-cyclohexadiene.



°C);<sup>21</sup> however, with experimental uncertainty, it is unclear if there is, in fact, a meaningful variance in the two rates.



22

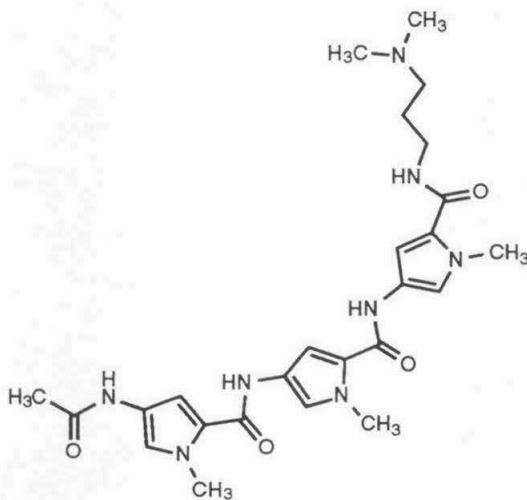


23 and 24

## DNA Binding and Cleavage Studies

The binding of conjugate **9** to double-stranded, B-form DNA was evaluated using the MPE•Fe(II) footprinting reagent of Dervan and co-workers<sup>7</sup> by determining the ability of **9** to protect against DNA cleavage within a 517 bp restriction fragment of plasmid pBR322 labeled, in separate experiments, with <sup>32</sup>P at the 5' and 3' termini. Dervan and co-workers have shown that this restriction fragment contains two preferred sites for the binding of the distamycin analog **25**.<sup>22</sup> Footprinting reactions were performed in

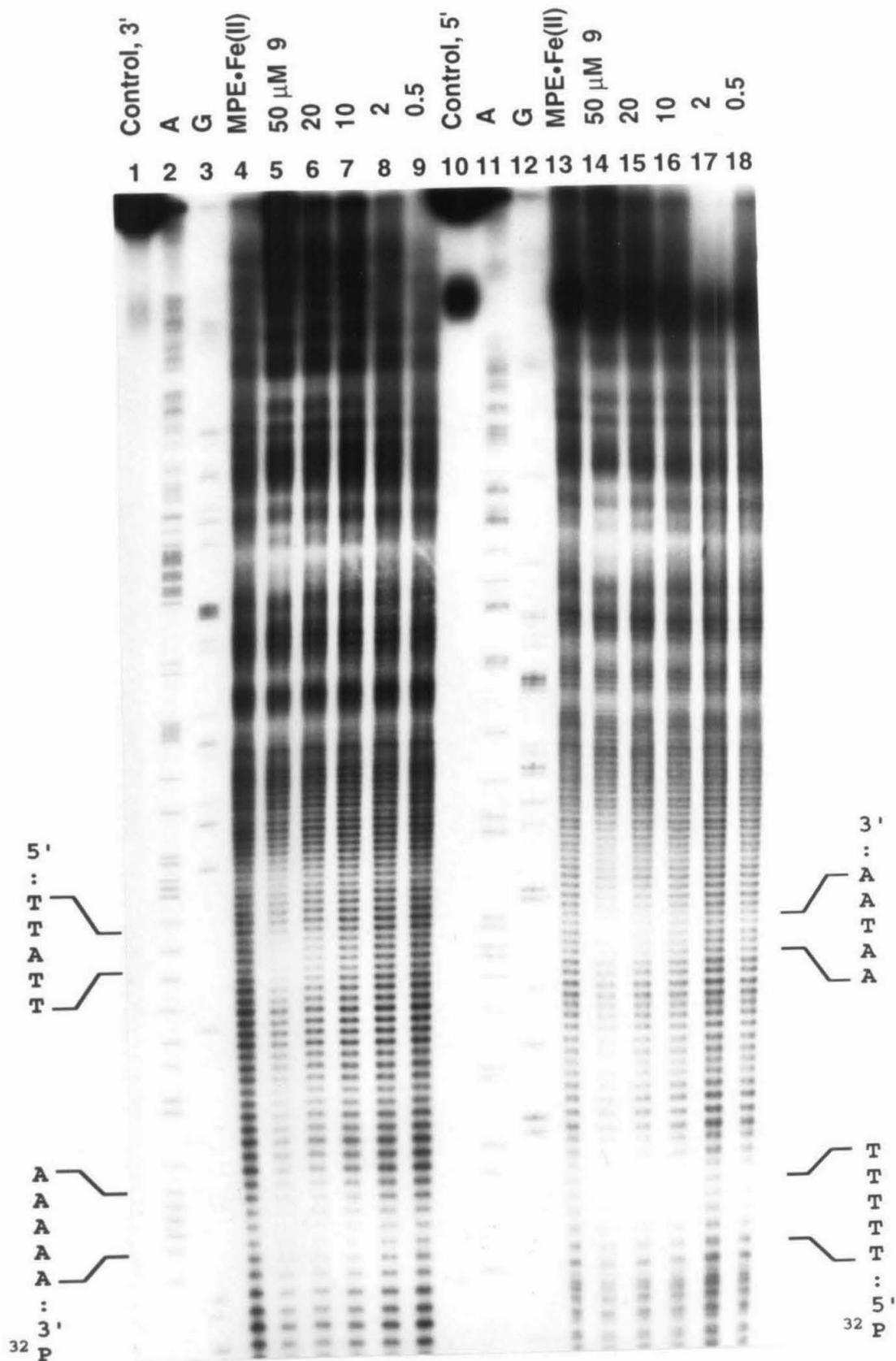
association buffer (10 mM NaCl, 25 mM Tris-acetate, pH 7.0) in the presence of double-stranded calf thymus DNA (100  $\mu$ M bp) at 37  $^{\circ}$ C across a range of concentrations of **9** (50–0.5  $\mu$ M) and were evaluated by gel electrophoresis using standard phosphor-imaging technology to reveal “footprints” of protection versus an MPE•Fe(II) control lane (Figure 3). Plotting of the data in histogram format shows that conjugate **9**, at a concentration of 10  $\mu$ M, protects two 5 bp sequences (5'-TTTTT-3' and 5'-AATAA-3') from cleavage by MPE•Fe(II) (Figure 4A). These sequences correspond to the areas of protection observed for the distamycin analog **25** and establish that the binding domain serves to confer sequence specific DNA binding to conjugate **9**, as anticipated.



**25**

Quantitative MPE•Fe(II) footprinting titrations<sup>26</sup> were performed to compare the relative DNA-binding affinities of the conjugate **9** and the distamycin analog **25** at the two designated protection sites. Footprinting reactions (as above) were conducted over a wide range of substrate concentrations (500  $\mu$ M to 1 nM for **9**; 100  $\mu$ M to 0.1 nM for **25**) and were analyzed by gel electrophoresis using standard phosphor-imaging technology to evaluate the data. From these data, binding affinities were calculated at each of the two binding sites (5'-TTTTT-3' and 5'-AATAA-3') for each substrate (the binding affinities are reported as relative, and not absolute, values due to the presence of calf thymus DNA in

**Figure 3.** Autoradiogram of an 8% denaturing polyacrylamide gel showing MPE•Fe(II) footprinting of **9**. All reaction mixtures contain calf thymus DNA (100  $\mu$ M bp), the end-labeled 517 bp restriction fragment of plasmid pBR322 (~18,000 cpm), and NaCl (10 mM) in Tris-acetate (25 mM, pH 7.0) buffer. Lanes 1–9 (3'-labeled DNA) contain intact DNA, A reaction,<sup>23</sup> Maxam–Gilbert G reaction,<sup>24</sup> and 0, 50, 20, 10, 2, and 0.5  $\mu$ M substrate **9**, respectively. Lanes 10–18 (5'-labeled DNA) contain intact DNA, A reaction,<sup>23</sup> Maxam–Gilbert G reaction,<sup>24</sup> and 0, 50, 20, 10, 2, and 0.5  $\mu$ M substrate **9**, respectively. Lanes 4–9 and 13–18 also contain MPE•Fe(II) (4  $\mu$ M) and dithiothreitol (4 mM).





**Figure 4.** (A) Histogram of footprinting patterns of protection by **9** (10  $\mu$ M, 37  $^{\circ}$ C, 15–25 min) from MPE•Fe(II) cleavage within a 517 bp restriction fragment of pBR322. Boxed sequences represent binding sites.<sup>25</sup> Shaded bars are proportional to the extent of protection from MPE•Fe(II) cleavage at the indicated base pair site. (B) Patterns of cleavage arising from **9** (10  $\mu$ M, 37  $^{\circ}$ C, 60–65 h) within the same 517 bp restriction fragment of pBR322. Boxed sequences designate the binding sites defined in the legend for (A) above. Arrow heights are proportional to the extent of cleavage at the indicated base pair site.

these experiments, Table 1). Inspection of the data shows that conjugate **9** binds with higher affinity at the 5'-TTTTT-3' site than at the 5'-AATAA-3' site, the same order of binding preference displayed by distamycin analog **25**.<sup>27</sup> Importantly, the data of Table 1 show that **9** binds some 30 times more weakly than the distamycin analog **25** (5'-AATAA-3' site), despite the larger size and greater hydrophobicity of **9**. This may reflect a poor fit of the allene-ene-yne cleaving domain of **9** into the minor groove of DNA, a feature which might explain, in part, the poor DNA cleavage efficiency of **9** (vide infra). Variation of the linking domain may well lead to improved DNA binding (and cleavage efficiency) in future conjugate molecules.

**Table 1.** Relative binding affinities of **9** and **25**.<sup>a</sup>

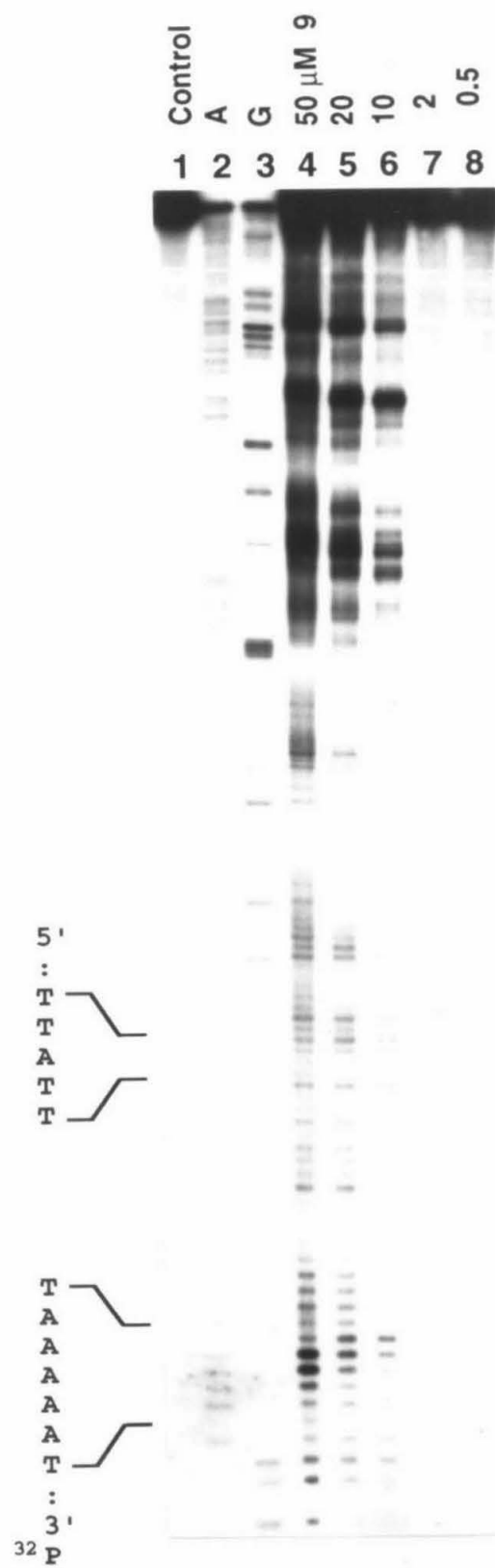
| Substrate                   | Binding Site     |             |
|-----------------------------|------------------|-------------|
|                             | 5'-TTTTT-3'      | 5'-AATAA-3' |
| distamycin analog <b>25</b> | 212 <sup>b</sup> | 29          |
| conjugate <b>9</b>          | 2.4              | 1.0         |

<sup>a</sup>Determined from binding isotherms generated from three separate MPE•Fe(II) quantitative footprinting experiments comparing the binding of **9** and **25** under identical conditions (100  $\mu$ M calf thymus DNA, 25 mM Tris-acetate (pH 7.0), 10 mM NaCl).

<sup>b</sup>The binding isotherm for this site, which is part of a 10 bp AT tract, exhibits two inflection points; the first value (tighter-binding) is reported.

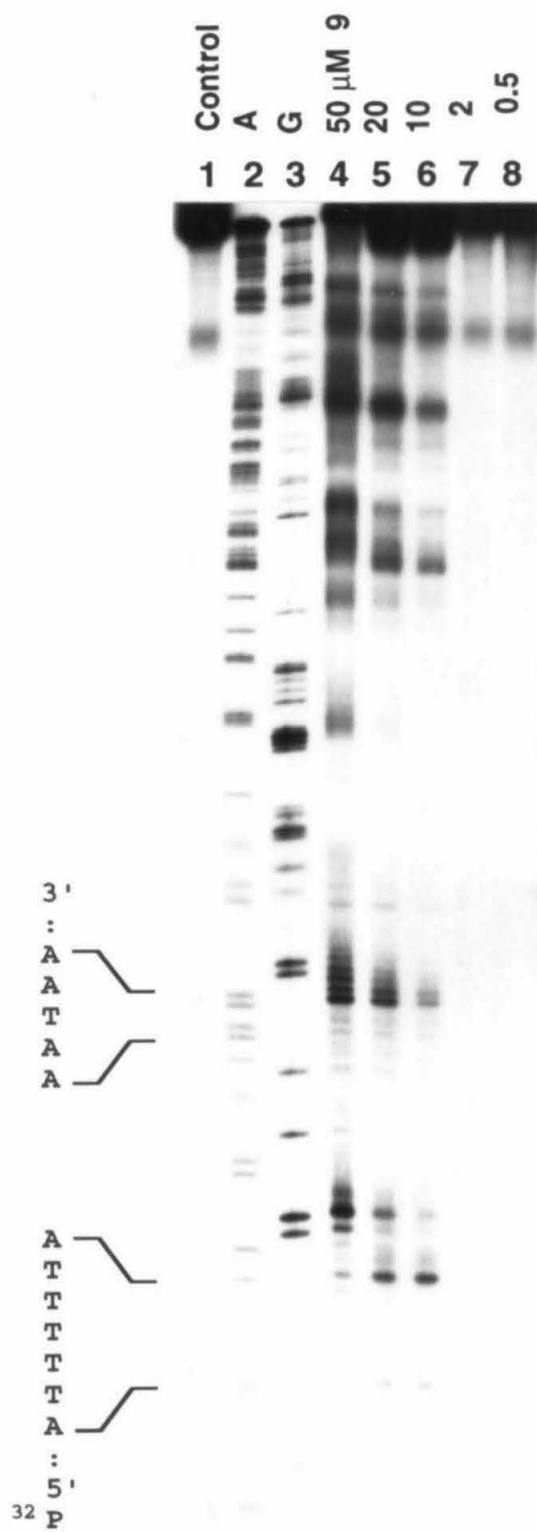
The ability of **9** to cleave double-stranded B-form DNA was probed using the 3'- and 5'-<sup>32</sup>P-labeled 517 bp restriction fragment of plasmid pBR322 described above in the footprinting studies. Cleavage reactions employed the conjugate **9** (50–0.5  $\mu$ M), calf thymus DNA (100  $\mu$ M bp), and 3'- or 5'-radiolabeled restriction fragment (~18,000 cpm) and were performed in association buffer (10 mM NaCl, 25 mM Tris-acetate, pH 7.0) at 37 °C for 60–65 h. DNA cleavage was assayed by gel electrophoresis using standard phosphor-imaging technology to quantitate cleavage at each base pair site (Figures 5 and 6). The gel data are translated into histogram format in Figure 4B. The minimum cleavage

**Figure 5.** DNA cleavage brought about by thermal reaction (37 °C, 60–65 h) with bioconjugate **9**. Autoradiogram of an 8% denaturing polyacrylamide gel. All reaction mixtures contain calf thymus DNA (100  $\mu$ M bp), the 3'-labeled 517 bp restriction fragment (~18,000 cpm), and NaCl (10 mM) in Tris-acetate (25 mM, pH 7.0) buffer. Lanes 1–8 contain intact DNA, A reaction,<sup>23</sup> Maxam–Gilbert G reaction,<sup>24</sup> and 50, 20, 10, 2, and 0.5  $\mu$ M substrate **9**, respectively.





**Figure 6.** DNA cleavage brought about by thermal reaction (37 °C, 60–65 h) with bioconjugate **9**. Autoradiogram of an 8% denaturing polyacrylamide gel. All reaction mixtures contain calf thymus DNA (100 µM bp), the 5'-labeled 517 bp restriction fragment (~18,000 cpm), and NaCl (10 mM) in Tris-acetate (25 mM, pH 7.0) buffer. Lanes 1–8 contain intact DNA, A reaction,<sup>23</sup> Maxam–Gilbert G reaction,<sup>24</sup> and 50, 20, 10, 2, and 0.5 µM substrate **9**, respectively.



efficiency, calculated by integration of all migrating radiolabeled fragments against total radioactivity, was 0.2%. This value contrasts with cleavage efficiencies of 5.7% for dynemicin A,<sup>28</sup> 25% for neocarzinostatin chromophore,<sup>29</sup> and ~90% for calicheamicin  $\gamma_1$ ,<sup>30</sup> all members of the enediyne class of natural products, and, as discussed above, may be due, in part, to a poor fit of the effector domain into the minor groove of DNA. The observed patterns of cleavage by **9** do not resemble typical patterns produced by diffusible cleaving agents and are site selective, exhibiting a preference for the 3'-side of each of the two binding sites defined in the footprinting studies above. This contrasts with the behavior of the affinity cleaving agent distamycin•EDTA,<sup>31</sup> which produces a "Gaussian" cleavage pattern typical of diffusible cleaving agents and shows a bias for cleavage toward the 5' side of the 5'-AATAA-3' site. The time course of DNA cleavage by **9** was studied by gel electrophoresis of a parallel series of cleavage reactions conducted as above, but with varied reaction periods (0–60 h). Analysis of the data shows that DNA cleavage increases linearly for the first 20 h of the reaction before slowing. This time course parallels the observed half-life for the cyclization of **9**, as required by a mechanism wherein DNA cleavage is brought about by an  $\alpha,3$ -dehydrotoluene intermediate.

The sequence selectivity of DNA cleavage by **9** exhibits an interesting variation as a function of the concentration of **9** (Figures 5 and 6). At the highest concentration of **9** (50  $\mu$ M), the cleavage pattern is clearly shifted versus that produced by a reaction employing 10  $\mu$ M **9**. One explanation for this shift could be that more than one conjugate molecule binds to the DNA-binding site at higher concentrations of conjugate. The binding of distamycin analogs as dimeric species at elevated concentrations has precedent.<sup>32</sup> Shifting of the protection pattern in footprinting studies of **9** (Figure 3) is also evident at the highest concentration of **9** (50  $\mu$ M).

The evaluation of single-stranded versus double-stranded DNA cleavage products from the reaction of conjugate **9** with the 3'-radiolabeled 517 bp restriction fragment, as described above, was conducted by non-denaturing gel electrophoresis. There was no

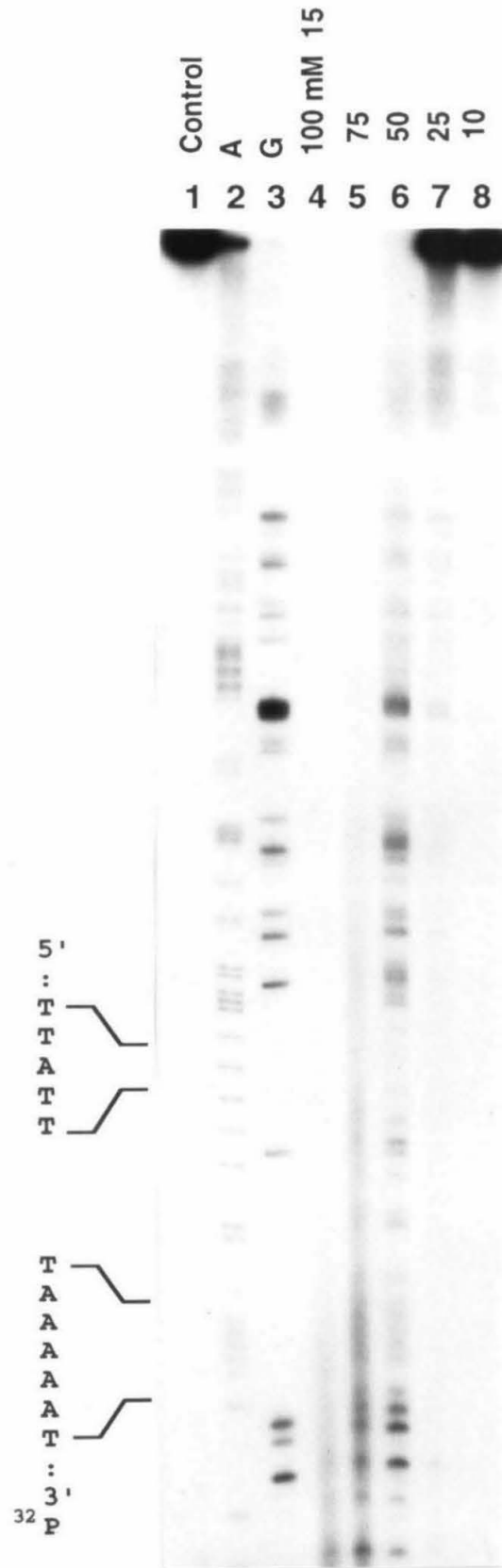
evidence of double-stranded DNA cleavage (data not shown). This result is consistent with the idea that DNA cleavage is brought about by an  $\alpha,3$ -dehydrotoluene biradical with a single highly reactive radical site; however, given the poor cleavage efficiency overall, the likelihood of a double-stranded nick is remote from a simple probabilistic view as well.

As a control, the parent (Z)-allene-ene-yne alcohol **15** was tested for DNA cleaving activity. Cleavage trials were performed over a range of concentrations of **15** (100–10 mM) with the 3'-radiolabeled 517 bp DNA restriction fragment of pBR322 described above and calf thymus DNA (100  $\mu$ M bp) in association buffer (10 mM NaCl, 25 mM Tris-acetate, pH 7.0) at 37 °C for 60–65 h and were evaluated using gel electrophoresis (Figure 7). DNA cleavage with **15** was apparent only at concentrations of 25 mM or greater, or some 2000 times higher than concentrations necessary for observable cleavage by the conjugate **9**. In addition, the cleavage pattern exhibited a preference for cleavage at A and G sites, suggesting a possible change in the cleavage mechanism, e.g., alkylative depurination. The data strongly support the view that the DNA-binding element is critical for the sequence-specific cleavage of DNA by **9** at micromolar concentrations.

## Conclusions

The studies presented here describe the synthesis and characterization of bioconjugate **9** as a mimic of the enediyne antibiotics. The conjugate **9** has been shown to bind and cleave DNA with sequence selectivity. The binding domain has been shown to localize the allene-ene-yne effector domain for sequence-selective DNA cleavage at micromolar concentrations of substrate. The time course of DNA cleavage parallels the rate of cyclization of **9** to form an  $\alpha,3$ -dehydrotoluene biradical. The pattern of DNA cleavage by **9** is suggestive of a nondiffusible cleaving agent. Although the data are consistent with the view that DNA cleavage arises from hydrogen-atom abstraction by a localized  $\alpha,3$ -dehydrotoluene biradical, the mechanism of DNA cleavage by **9** has by no means been established. Importantly, it has been shown that the (Z)-allene-ene-yne functional group is

**Figure 7.** DNA cleavage brought about by thermal reaction (37 °C, 60–65 h) with alcohol **15**. Autoradiogram of an 8% denaturing polyacrylamide gel. All reaction mixtures contain calf thymus DNA (100 µM bp), the 3'-labeled 517 bp restriction fragment (~18,000 cpm), and NaCl (10 mM) in Tris-acetate (25 mM, pH 7.0) buffer. Lanes 1–8 contain intact DNA, A reaction,<sup>23</sup> Maxam-Gilbert G reaction,<sup>24</sup> and 100, 75, 50, 25, and 10 mM substrate **15**, respectively.



a viable effector domain for DNA cleavage upon mild thermal activation. The efficiency of DNA cleavage by **9** is poor and may reflect less than optimum positioning of the effector domain in the minor groove of DNA. This speculation receives some support from the fact that the conjugate **9** binds ca. 30 times more weakly to DNA than the smaller, less hydrophobic distamycin analog **25**. This observation also suggests that future studies may benefit from modification of the linking domain.

## Experimental Section

**General Procedures.** All reactions were performed in flame-dried round bottom or modified Schlenk (Kjeldahl shape) flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Where necessary (so noted), reaction mixtures were degassed by alternate evacuation/argon-flush cycles (five or more iterations). Organic solutions were concentrated by rotary evaporation at ~25 Torr (water aspirator). Flash chromatography was performed as described by Still et al.,<sup>33</sup> employing 230–400 mesh silica gel. Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel containing a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light and/or exposure to an acidic solution of *p*-anisaldehyde followed by heating on a hot plate. NMR tubes for sealed tube experiments were fabricated by attachment of a standard 18 cm [5 mm outside diameter (o.d.)] NMR tube to a standard taper female 14/20 joint using a 7 cm extension of 5 mm o.d. medium-wall borosilicate glass. Sealed NMR samples were prepared by flame-sealing a frozen (liquid nitrogen), evacuated ( $\leq 10$  mTorr) sample that had been degassed by five successive freeze–pump–thaw cycles.

**Materials.** Commercially available reagents were used as received with the following exceptions. Diethyl ether and tetrahydrofuran were distilled from sodium benzophenone ketyl. Benzene, toluene, dichloromethane, triethylamine, *N,N*-diisopropylethylamine, and hexanes were distilled from calcium hydride at 760 Torr. Methanol was distilled from magnesium at atmospheric pressure. Methanesulfonyl chloride was distilled from phosphorus pentoxide at atmospheric pressure. Anhydrous *N,N*-dimethylformamide was purchased from Aldrich Chemical Co. and was stored over 4Å molecular sieves. Cuprous iodide was purified by continuous extraction (48 hours)



with tetrahydrofuran in a Soxhlet apparatus. 1,4-Cyclohexadiene was purified by passage through a short column of neutral alumina immediately prior to use.

**Instrumentation.** Infrared (IR) spectra were obtained using a Perkin-Elmer 1600 FT-IR spectrophotometer internally referenced to a polystyrene standard. Data are presented as follows: frequency of absorption ( $\text{cm}^{-1}$ ), intensity of absorption (s = strong, m = medium, w = weak, br = broad), and assignment (where appropriate). Proton nuclear magnetic resonance ( $^1\text{H}$  NMR) and carbon nuclear magnetic resonance ( $^{13}\text{C}$  NMR) spectra were obtained on General Electric QE-300 (300 MHz), JEOL JX-400 (400 MHz), or Bruker AM-500 (500 MHz) NMR spectrometers; chemical shifts are expressed in parts per million ( $\delta$  scale) relative to an internal standard of chloroform ( $^1\text{H}$ , 7.26;  $^{13}\text{C}$ , 77.0), benzene- $d_6$  ( $^1\text{H}$ , 7.20;  $^{13}\text{C}$ , 128.0), or dimethyl sulfoxide- $d_6$  ( $^1\text{H}$ , 2.49;  $^{13}\text{C}$ , 39.5). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet, ABq = AB quartet), integration, coupling constant in hertz (Hz), and assignment. High resolution mass spectra (HRMS) were obtained at the University of California, Riverside, Mass Spectrometry Facility or at the University of Nebraska, Lincoln, Midwest Center for Mass Spectrometry (with partial support by the National Science Foundation, Biology Division, Grant DIR9017262). High pressure liquid chromatography (HPLC) purification was carried out on a Waters Delta Prep 3000 instrument equipped with a Waters 994 programmable photodiode array detector using Vydac analytical (10  $\mu\text{m}$ , 0.46  $\times$  25 cm) and preparative (10  $\mu\text{m}$ , 2.2  $\times$  25 cm) reverse-phase C18 (201HS) columns. UV spectra were obtained on a Shimadzu UV160U spectrophotometer.

**Reagents and Materials for DNA Studies.** All reaction solutions were prepared with ultrapure water, obtained from a Millipore Milli-Q Plus water purification system. Sonicated, deproteinized calf thymus DNA was purchased from Pharmacia and was dissolved in water to a concentration of 1 mM base pairs (bp) in DNA. Plasmid pBR322 was purchased from Boehringer-Mannheim. Enzymes were obtained from

Boehringer-Mannheim and New England Biolabs and were used with the supplied buffers, with the exception of Klenow enzyme, which was used with *Hae*III buffer. Deoxyadenosine 5'-[ $\alpha$ - $^{32}$ P]triphosphate and adenosine 5'-[ $\gamma$ - $^{32}$ P]triphosphate were purchased from Amersham or NEN. Other reagents were used as received. Standard techniques were employed for DNA manipulations.<sup>34</sup>

**DNA Fragment Preparation.** Plasmid pBR322 was linearized with *Eco*RI restriction endonuclease and then was labeled on the 3' terminus with [ $\alpha$ - $^{32}$ P]dATP using the Klenow fragment of DNA polymerase I. Following removal of the 5'-phosphate with calf alkaline phosphatase (CAP), a separate batch of *Eco*RI-digested plasmid was labeled at the 5' end with [ $\gamma$ - $^{32}$ P]ATP using T4 polynucleotide kinase. After labeling, the DNA was digested with *Rsa*I to yield two end-labeled restriction fragments. The 517 bp fragment was excised from a 5% non-denaturing polyacrylamide gel (17.0  $\times$  15.0 cm  $\times$  3 mm thickness) and further isolated according to standard procedures.<sup>34</sup> Chemical-sequencing reactions were performed according to published methods.<sup>23,24</sup> A molecular weight standard for the non-denaturing gels was prepared as follows. Equal amounts of the 3'-radiolabeled 517 bp fragment and 0.25  $\mu$ g of pBR322 were combined and digested individually with restriction endonucleases *Ssp*I, *Bsp*HI, and *Xmn*I. The reaction mixtures were ethanol precipitated, counted, diluted to the same concentration [counts per minute (cpm) per microliter], and then combined in equal volumes with the same cpm of intact 517 bp fragment.

**Footprinting and Cleavage Reactions.** Reactions were executed in a total volume of 20  $\mu$ L with final concentrations of each component as noted. The conjugate **9** was added to solutions of radiolabeled restriction fragment (~18,000 cpm), calf thymus DNA (100  $\mu$ M bp), Tris-acetate buffer (25 mM, pH 7.0), and NaCl (10 mM), and the resulting solutions were incubated for 15 min at 37  $^{\circ}$ C. Footprinting reactions were initiated by addition of MPE•Fe(II) solution (4  $\mu$ M, prepared by mixing 20  $\mu$ L of a 100  $\mu$ M MPE solution with 20  $\mu$ L of a freshly made, 100  $\mu$ M ferrous ammonium sulfate solution

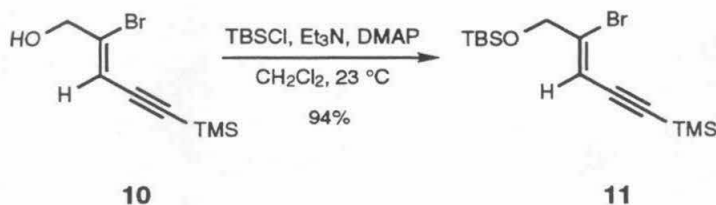
and then diluting to 100  $\mu$ L with water)<sup>35</sup> and dithiothreitol (4 mM) and proceeded for 9 min at 37 °C. Cleavage reactions were incubated at 37 °C for various defined lengths of time, up to 70 h. All reactions were terminated by freezing (dry ice), and the frozen solution was lyophilized on a Savant rotary speed-vac. The reaction mixtures were resuspended in 80% denaturing formamide loading buffer (4  $\mu$ L), assayed for radioactivity (Beckman LS 6000SC scintillation counter), and electrophoresed on 8% polyacrylamide denaturing gels (5% crosslink, 7 M urea; 31  $\times$  38.5 cm  $\times$  0.4 mm thickness) at 1700 V for 1.5 h. The gels were dried and analyzed using standard phosphor technology. Dried gels were also exposed to preflashed X-ray film at -80 °C with an intensifying screen.

**Quantitative MPE•Fe(II) Footprint Titrations.** Reaction mixtures (20  $\mu$ L total volume) consisted of the following final concentrations: serially diluted conjugate **9** (500  $\mu$ M to 1 nM) or distamycin analog **25** (100  $\mu$ M to 0.1 nM), 3'-labeled 517 bp restriction fragment (20,000 cpm), calf thymus DNA (100  $\mu$ M bp), Tris-acetate buffer (25 mM, pH 7.0), and NaCl (10 mM). After incubation at 37 °C for 15 min, freshly prepared MPE•Fe(II) solution (2  $\mu$ M) and dithiothreitol (2 mM) were added to initiate the footprinting reactions. After the reactions proceeded for 9 min at 37 °C, the mixtures were frozen (dry ice) and dried by speed-vac. Reaction mixtures were electrophoresed and analyzed as described above.

**Calculation of Relative Binding Affinities.** Binding isotherms were created following published methods.<sup>26</sup> Briefly, standard phosphor-imaging technology was used to analyze both binding sites (5'-TTTTT-3' and 5'-AATAA-3') and a reference site (5'-CGTCA-3') by performing volume integrations. The apparent fraction of DNA bound ( $\theta_{app}$ ) was calculated and then fit to a Langmuir binding titration isotherm over the range of substrate concentrations. Binding affinities were determined from averaged  $\theta_{app}$  values from three different acceptable (according to the  $\chi^2$  criterion)<sup>36</sup> gels. Values from the two binding sites were then compared for conjugate **9** and the distamycin analog **25**.

**Cleavage Trials under Non-denaturing Conditions.** Reactions were executed in a total volume of 20  $\mu$ L with the final concentrations of each component as follows, coupled product **9** (20 or 10  $\mu$ M), 3'-labeled 517 bp restriction fragment (8,000 cpm), calf thymus DNA (100  $\mu$ M bp), Tris-acetate buffer (25 mM, pH 7.0), and NaCl (10 mM), and incubated at 37 °C for 60–70 h. Reactions were terminated by ethanol precipitation, and mixtures were dried on a rotary speed-vac. The dried pellet was resuspended in water (10  $\mu$ L) and Ficoll (6 $\times$ ) loading buffer (2  $\mu$ L), and the resulting suspension was assayed for radioactivity. Samples were electrophoresed on an 8% non-denaturing polyacrylamide gel (125 V, 17.0  $\times$  15.0 cm  $\times$  1.5 mm thickness) positioned behind a cooling fan until the bromophenol blue dye had migrated within 1–2 cm of the bottom of the gel. The gel was then exposed to preflashed X-ray film at –80 °C with an intensifying screen.

**Quantitation by Storage Phosphor Technology Autoradiography.** Photostimulatable storage phosphor-imaging plates (Kodak S0230) were pressed flat against dried gels and exposed in the dark at 23 °C for 12–18 h. Data from storage plates were obtained from a Molecular Dynamics 400S PhosphorImager. Data analysis was performed by calculation of volume integrations of all bands using the ImageQuant v.3.1 software running on an AST Premium 386/33 computer.



*tert*-Butyldimethylsilyl chloride (0.895 g, 5.95 mmol, 1.1 equiv) was added to a solution of alcohol **10** (1.26 g, 5.41 mmol, 1 equiv)<sup>4</sup> and triethylamine (1.14 mL, 8.12 mmol, 1.5 equiv) in dichloromethane (100 mL) at 0 °C. After 5 min, the reaction mixture was warmed to 23 °C, 4-dimethylaminopyridine (0.179 g, 1.46 mmol, 0.27 equiv) was added, and the resulting solution was stirred for 17 h. The reaction mixture was then poured into water (100 mL), and the product was extracted with a 1:1 mixture of ethyl acetate and hexanes (3 × 150 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash chromatography (5% ethyl acetate–hexanes) to yield the (*Z*)-bromoene **11** (1.76 g, 94%) as a yellow oil.

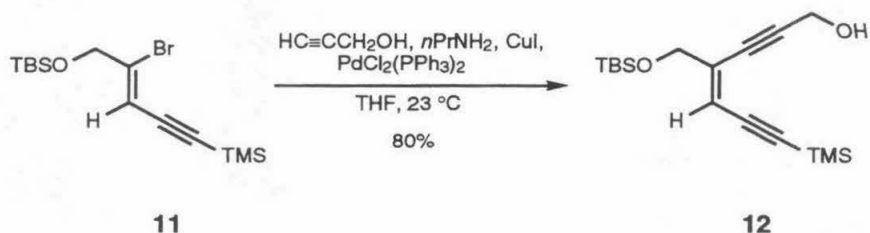
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), δ: 6.38 (t, 1 H, *J* = 2.0 Hz, C=CH), 4.31 (d, 2 H, *J* = 2.0 Hz, SiOCH<sub>2</sub>), 0.92 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 0.24 (s, 9H, Si(CH<sub>3</sub>)<sub>3</sub>), 0.10 (s, 6H, Si(CH<sub>3</sub>)<sub>2</sub>)

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>), δ: 137.2 (CH=CBr), 108.8 (CH=CBr), 101.2 (C≡C), 101.1 (C≡C), 67.5 (CH<sub>2</sub>OTBS), 25.7 (SiC(CH<sub>3</sub>)<sub>3</sub>), 22.6 (SiC(CH<sub>3</sub>)<sub>3</sub>), -0.2 (Si(CH<sub>3</sub>)<sub>3</sub>), -5.5 (Si(CH<sub>3</sub>)<sub>2</sub>)

FTIR (neat), cm<sup>-1</sup>: 2956 (s), 2858 (m), 2145 (m, C≡C), 1471 (m), 1375 (m), 1251 (s), 1132 (s), 1092 (s), 1032 (m), 842(s), 779(m)

HRMS (CI): Calc'd for C<sub>14</sub>H<sub>28</sub>BrOSi<sub>2</sub> [M + H]<sup>+</sup>: 347.0863  
Found: 347.0849

TLC (20% EtOAc in hexanes), *R<sub>f</sub>*: 0.89

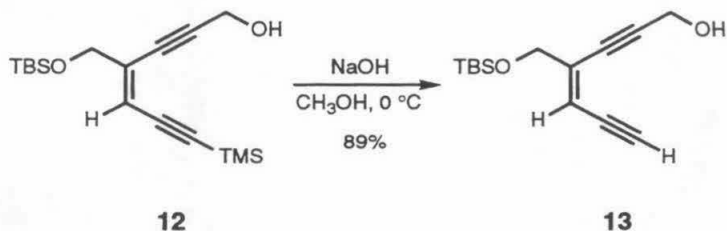


A solution of the (Z)-bromoene **11** (1.76 g, 5.07 mmol, 1 equiv), propargyl alcohol (0.58 mL, 10.1 mmol, 2.0 equiv), and *n*-propylamine (1.67 mL, 20.3 mmol, 4.0 equiv) in tetrahydrofuran (50 mL) was deoxygenated at 23 °C and then was cooled in ice. Cuprous iodide (0.145 g, 0.760 mmol, 0.15 equiv) and bis(triphenylphosphine)palladium(II) chloride (0.178 g, 0.254 mmol, 0.05 equiv) were added sequentially to the reaction mixture, deoxygenating thoroughly after each addition. Upon completed addition, the reaction mixture was warmed from 0 to 23 °C and then was stirred for 15 h. The reaction mixture was poured into a 1:1 mixture of saturated aqueous ammonium chloride solution and saturated aqueous potassium carbonate solution (60 mL). The product was extracted with a 1:1 mixture of ethyl acetate and hexanes (3 × 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash chromatography (10% ethyl acetate–hexanes) to give the (Z)-enediynes **12** (1.31 g, 80%) as an oil.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>), δ: 6.06 (t, 1H, *J* = 2.1 Hz, C=CH), 4.46 (s, 2H, C≡CCH<sub>2</sub>OH), 4.20 (d, 2H, *J* = 2.1 Hz, SiOCH<sub>2</sub>R), 0.91 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 0.22 (s, 9H, Si(CH<sub>3</sub>)<sub>3</sub>), 0.07 (s, 6H, Si(CH<sub>3</sub>)<sub>2</sub>)

|   |                                   |  |       |
|---|-----------------------------------|--|-------|
| $^{13}\text{C}$ NMR (125 MHz, $\text{CDCl}_3$ ), $\delta$ : | 135.0 (RCH=C),                    | 113.3 (RCH=C),                         | 102.4 |
|   | (C $\equiv$ CTMS),                | 101.7 (C $\equiv$ CTMS),               | 95.5  |
|   | (C $\equiv$ CCH <sub>2</sub> OH), | 82.1 (C $\equiv$ CCH <sub>2</sub> OH), | 64.5  |
|   | (RCH <sub>2</sub> OTBS),          | 51.6 (RCH <sub>2</sub> OH),            | 25.8  |

|  |  |
|--|--|
|  | (SiC(CH <sub>3</sub> ) <sub>3</sub> ), 18.3 (SiC(CH <sub>3</sub> ) <sub>3</sub> ), -0.1 (Si(CH <sub>3</sub> ) <sub>3</sub> ),<br>-5.5 (Si(CH <sub>3</sub> ) <sub>2</sub> ) |
| FTIR (neat), cm <sup>-1</sup> :              | 3358 (br, OH), 2956 (s), 2858 (m), 2134 (m,<br>C≡C), 1469 (w), 1252 (s), 1120 (s), 1034 (w),<br>851 (s), 778 (m)   |
| HRMS (CI):                                   | Calc'd for C <sub>17</sub> H <sub>31</sub> O <sub>2</sub> Si <sub>2</sub> [M + H] <sup>+</sup> : 323.1862<br>Found: 323.1859   |
| TLC (20% EtOAc in hexanes), R <sub>f</sub> : | 0.38   |



Aqueous sodium hydroxide solution (50% w/w, total volume 0.25 mL) was added in five portions over a 2 h period to an ice-cooled solution of the (*Z*)-enediynone **12** (0.650 g, 2.02 mmol, 1 equiv) in methanol (25 mL). The reaction mixture was then poured into water (100 mL), and the product was extracted with a 1:1 mixture of ethyl acetate and hexanes (3 × 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash chromatography (20% ethyl acetate–hexanes) to provide the (*Z*)-enediynone **13** as an oil (0.45 g, 89%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 6.04 (dd, 1H,  $J = 4.5$  Hz, 2.1 Hz,  $\text{C}=\text{CH}$ ), 4.47 (d, 2H,  $J = 6.0$  Hz,  $\text{RCH}_2\text{OH}$ ), 4.22 (d, 2H,  $J = 1.5$  Hz,  $\text{SiOCH}_2$ ), 3.29 (m, 1H,  $\text{C}\equiv\text{CH}$ ), 1.62 (t, 1H,  $J = 6.1$  Hz,  $\text{RCH}_2\text{OH}$ ), 0.92 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 0.08 (s, 6H,  $\text{Si}(\text{CH}_3)_2$ )

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 135.6 ( $\text{RCH}=\text{C}$ ), 112.0 ( $\text{RCH}=\text{C}$ ), 95.5 ( $\text{C}\equiv\text{CCH}_2\text{OH}$ ), 83.6 ( $\text{C}\equiv\text{CH}$ ), 81.7 ( $\text{C}\equiv\text{CCH}_2\text{OH}$ ), 81.0 ( $\text{C}\equiv\text{CH}$ ), 64.6 ( $\text{RCH}_2\text{OTBS}$ ), 51.6 ( $\text{RCH}_2\text{OH}$ ), 25.8 ( $\text{SiC}(\text{CH}_3)_3$ ), 18.3 ( $\text{SiC}(\text{CH}_3)_3$ ), -5.5 ( $\text{Si}(\text{CH}_3)_2$ )

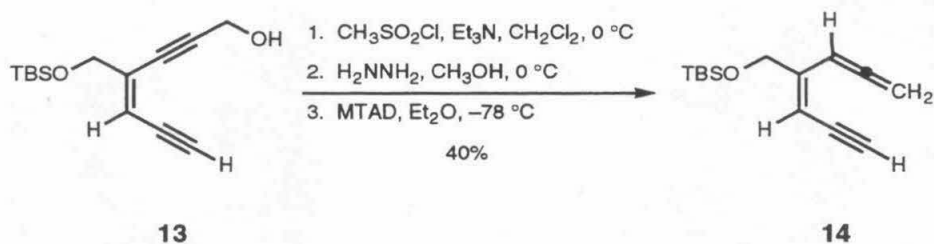
FTIR (neat),  $\text{cm}^{-1}$ : 3289 (br, OH, and s,  $\text{C}\equiv\text{CH}$ ), 2932 (s), 2858 (s), 2217 (w), 2103 (w), 1467 (m), 1257 (s), 1118 (s), 1032 (m), 840 (s), 780 (s)

HRMS (FAB): Calc'd for  $\text{C}_{14}\text{H}_{22}\text{NaO}_2\text{Si}$  [ $\text{M} + \text{Na}$ ] $^+$ : 273.1287



Found: 273.1284

TLC (20% EtOAc in hexanes),  $R_f$ : 0.29

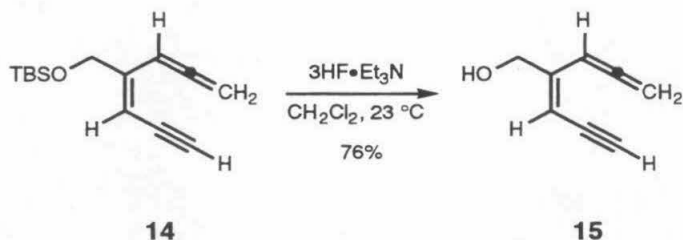


Methanesulfonyl chloride (0.17 mL, 2.3 mmol, 3.0 equiv) was added dropwise over 10 min to an ice-cooled solution of the (*Z*)-enediyne **13** (0.19 g, 0.75 mmol, 1 equiv) and triethylamine (0.55 mL, 3.8 mmol, 5.0 equiv) in dichloromethane (8 mL). The resulting suspension was stirred for 15 min at 0 °C. A solution of anhydrous hydrazine in methanol (1:1 v/v, 1.5 mL, 23.9 mmol hydrazine, 31.8 equiv) was then added directly by syringe, and the reaction mixture was stirred at 0 °C for 18 h. The reaction solution was poured into half-saturated brine (100 mL), and the product alkylhydrazine was extracted with 5% methanol in dichloromethane (2 × 100 mL). The combined organics were washed with brine (100 mL), dried over sodium sulfate, and concentrated in vacuo.

The crude alkylhydrazine (theory, 0.75 mmol, 1 equiv) was taken up in diethyl ether (70 mL), and the resulting solution was deoxygenated at 23 °C and then was cooled to −78 °C. A deoxygenated solution of 4-methyl-1,2,4-triazoline-3,5-dione (MTAD, 0.170 g, 1.5 mmol, 2.0 equiv) in diethyl ether (10 mL) was added quickly to the reaction mixture via cannula. The resulting pink solution was stirred at −78 °C for 15 min and was then poured into half-saturated brine (150 mL). The product allene was extracted with pentane (3 × 200 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash chromatography (5% ethyl acetate–hexanes), affording the allene **14** (70.0 mg, 40%) as a yellow oil.

$^1\text{H}$  NMR (400 MHz,  $\text{C}_6\text{D}_6$ ),  $\delta$ : 6.86 (t, 1H,  $J = 6.8$  Hz,  $\text{HC}=\text{C}=\text{CH}_2$ ), 6.08 (s, 1H,  $\text{C}=\text{CH}$ ), 4.69 (d, 2H,  $J = 6.8$  Hz,  $\text{HC}=\text{C}=\text{CH}_2$ ), 4.35 (s, 2H,  $\text{SiOCH}_2$ ), 2.98 (s,

|   |  |
|---|--|
|   | 1H, C≡CH), 0.94 (s, 9H, SiC(CH <sub>3</sub> ) <sub>3</sub> ), 0.01 (s, 6H, Si(CH <sub>3</sub> ) <sub>2</sub> )   |
| <sup>13</sup> C NMR (100 MHz, C <sub>6</sub> D <sub>6</sub> ), δ: | 210.5 (C=C=C), 146.5 (RCH=C), 104.2 (RCH=C), 90.8 (C=C=CH <sub>2</sub> ), 84.6 (C≡CH), 81.0 (C≡CH), 78.3 (C=C=CH <sub>2</sub> ), 62.9 (RCH <sub>2</sub> OTBS), 26.0 (SiC(CH <sub>3</sub> ) <sub>3</sub> ), 18.4 (SiC(CH <sub>3</sub> ) <sub>3</sub> ), -5.5 (Si(CH <sub>3</sub> ) <sub>2</sub> ) |
| FTIR (neat), cm <sup>-1</sup> :                                   | 3310 (m), 2955 (s), 2929 (s), 2857 (s), 2100 (w), 1934 (m), 1666(w), 1604 (w), 1464 (m), 1390 (w), 1362 (w), 1255 (s), 1192 (m), 1118 (s), 1076 (m), 1006 (w), 939 (w), 841 (s), 778 (s), 671 (w), 638 (w)   |
| HRMS (CI):  | Calc'd for C <sub>14</sub> H <sub>23</sub> OSi [M + H] <sup>+</sup> : 235.1518<br>Found: 235.1516  |
| TLC (50% EtOAc in hexanes), R <sub>f</sub> :                      | 0.93   |



A total volume of 1.75 mL of triethylamine trihydrofluoride was added in four portions over a period of 2 h to a solution of the allene **14** (70.0 mg, 299  $\mu\text{mol}$ , 1 equiv) in dichloromethane (10 mL) at 23  $^\circ\text{C}$  with periodic monitoring of the progress of the reaction by thin-layer chromatography. After being stirred for an additional 1 h, the reaction mixture was poured into water (100 mL), and the product was extracted with dichloromethane ( $3 \times 100$  mL). The combined organics were dried over sodium sulfate and were concentrated. The residue was purified by flash chromatography (30% ethyl acetate–hexanes), providing the alcohol **15** as a (volatile) yellow oil (27.3 mg, 76%).

$^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ ),  $\delta$ : 6.76 (t, 1H,  $J = 6.7$  Hz,  $\text{HC}=\text{C}=\text{CH}_2$ ), 5.69 (s, 1H,  $\text{C}=\text{CH}$ ), 4.64 (d, 2H,  $J = 6.7$  Hz,  $\text{HC}=\text{C}=\text{CH}_2$ ), 3.93 (d, 2H,  $J = 5.6$  Hz,  $\text{HOCH}_2$ ), 2.96 (s, 1H,  $\text{C}\equiv\text{CH}$ ), 0.70 (t, 1H,  $J = 5.8$  Hz,  $\text{HOCH}_2$ )

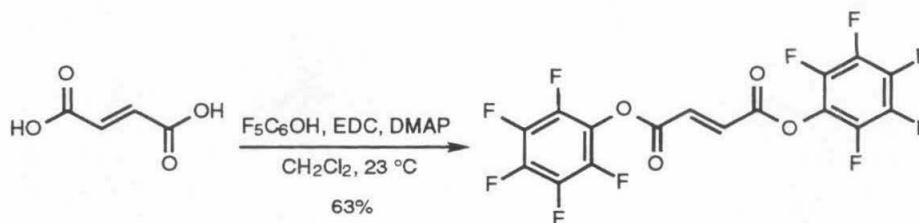
$^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 209.8 ( $\text{C}=\text{C}=\text{C}$ ), 147.4 ( $\text{RCH}=\text{C}$ ), 87.0 ( $\text{RCH}=\text{C}$ ), 87.0 ( $\text{C}=\text{C}=\text{CH}_2$ ), 80.6 ( $\text{RC}\equiv\text{CH}$ ), 79.1 ( $\text{RC}\equiv\text{CH}$ ), 75.6 ( $\text{C}=\text{C}=\text{CH}_2$ ), 60.5 ( $\text{CH}_2\text{OH}$ )

FTIR (neat),  $\text{cm}^{-1}$ : 3294 (br, OH, and s,  $\text{C}\equiv\text{C}$ ), 2924 (s), 2092 (w), 1932 (s,  $\text{C}=\text{C}=\text{C}$ ), 1718 (m), 1600 (w), 1385 (m), 1292 (m), 1056 (s), 852 (s)

HRMS (EI): Calc'd for  $\text{C}_8\text{H}_8\text{O}$   $[\text{M}]^+$ : 120.0575

Found: 120.0572

TLC (30% EtOAc in hexanes),  $R_f$ : 0.44

**20**

Fumaric acid (0.200 g, 1.72 mmol, 1 equiv), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 0.992 g, 5.16 mmol, 3.0 equiv), and 4-dimethylaminopyridine (7.5 mg, 61  $\mu$ mol, 0.04 equiv) were added sequentially to a solution of pentafluorophenol (0.955 g, 5.19 mmol, 3.0 equiv) in dichloromethane (50 mL). After being stirred at 23 °C for 12 h, the reaction mixture was poured into water (100 mL) and the product was extracted with dichloromethane (3  $\times$  100 mL). The combined organic layers were dried over sodium sulfate and were concentrated to a volume of 100 mL. The concentrated product solution was extracted with saturated aqueous sodium bicarbonate solution (3  $\times$  90 mL), was dried over sodium sulfate, and was concentrated. Upon addition of cold dichloromethane (−20 °C, 10 mL), the product precipitated as a pale yellow solid. The solid was collected, and the filtrate was concentrated. The residue upon concentration was precipitated with cold dichloromethane, as before, and the precipitate was collected and combined with the first crop of product. The solid product was dried under vacuum to provide 0.489 g (63%) of bis(pentafluorophenyl) ester **20** (mp 161–163.5 °C dec).

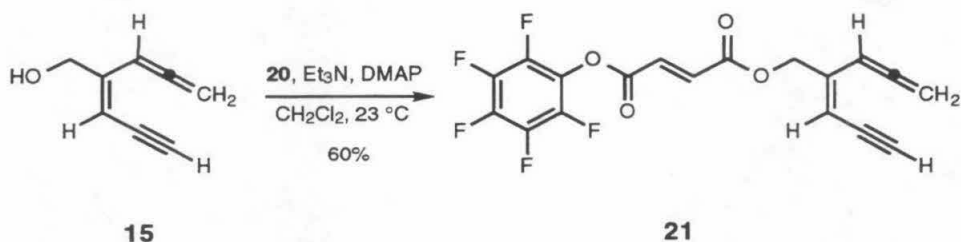
|   |   |
|---|---|
| $^1\text{H}$ NMR (400 MHz, $\text{CDCl}_3$ ), $\delta$ :    | 7.34 (s, 2H, $\text{CH}=\text{CH}$ )  |
| $^{13}\text{C}$ NMR (100 MHz, $\text{CDCl}_3$ ), $\delta$ : | 160.2 ( $\text{CO}_2\text{R}$ ), 134.0 ( $\text{C}(\text{O})\text{CH}=\text{CHC}(\text{O})$ ), 124–143 (complex, pentafluorophenyl carbons) |
| FTIR (neat), $\text{cm}^{-1}$ :                             | 3097 (w), 1769 (m), 1516 (s), 1324 (w), 1282 (s), 1120 (s), 1026 (w), 1002 (s), 907 (w)   |

HRMS (FAB):

Calc'd for  $\text{C}_{16}\text{H}_2\text{F}_{10}\text{O}_4$   $[\text{M}]^-$ : 447.9793

Found: 447.9823

TLC (0.4% AcOH in EtOAc),  $R_f$ : 0.94



Bis(pentafluorophenyl) ester **20** (0.286 g, 0.638 mmol, 3.0 equiv) and 4-dimethylaminopyridine (~2 mg, 20  $\mu\text{mol}$ , 0.01 equiv) were added sequentially to a pale yellow solution of alcohol **15** (25 mg, 210  $\mu\text{mol}$ , 1 equiv) and triethylamine (148  $\mu\text{L}$ , 1.07 mmol, 5.0 equiv) in dichloromethane (25 mL) at 23  $^\circ\text{C}$ . After stirring for 3.5 h at 23  $^\circ\text{C}$ , the reaction mixture was poured into water (90 mL), and the product was extracted with a 1:1 mixture of ethyl acetate and hexanes ( $3 \times 100$  mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash chromatography (20% toluene–hexanes) to provide 48 mg (60%) of pentafluorophenyl ester **21** as an oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 7.11 (ABq, 2H,  $J = 15.9$  Hz,  $\Delta\nu = 18.9$  Hz,  $\text{C}(\text{O})\text{CH}=\text{CHC}(\text{O})$ ), 6.54 (t, 1H,  $J = 7.2$  Hz,  $\text{HC}=\text{C}=\text{CH}_2$ ), 5.59 (s, 1H,  $\text{RCH}=\text{C}$ ), 5.13 (d, 2H,  $J = 6.8$  Hz,  $\text{C}=\text{C}=\text{CH}_2$ ), 4.86 (s, 2H,  $\text{CH}_2\text{OR}$ ), 3.36 (d, 1H,  $J = 2.4$  Hz,  $\text{C}\equiv\text{CH}$ )

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 211.0 ( $\text{C}=\text{C}=\text{C}$ ), 163.4 ( $\text{CO}_2\text{CH}_2$ ), 160.6 ( $\text{CO}_2\text{C}_6\text{F}_5$ ), 141.1 ( $\text{RCH}=\text{C}$ ), 137.0 and 130.4 ( $\text{C}(\text{O})\text{CH}=\text{CHC}(\text{O})$ ), 107.6 ( $\text{RCH}=\text{C}$ ), 90.9 ( $\text{C}=\text{C}=\text{CH}_2$ ), 85.5 ( $\text{RC}\equiv\text{CH}$ ), 79.5 ( $\text{RC}\equiv\text{CH}$ ), 79.2 ( $\text{C}=\text{C}=\text{CH}_2$ ), 65.0 ( $\text{CH}_2\text{OR}$ ), 124–143 (complex, pentafluorophenyl carbons)

FTIR (neat),  $\text{cm}^{-1}$ : 3294 (m), 3077 (w), 2995 (w), 2933 (w), 2667



(w), 2462 (w), 2092 (w), 1933 (m), 1773 (s),  
1732 (s), 1645 (m), 1604 (w), 1522 (s), 1471  
(w), 1376 (w), 1285 (s), 1201 (s), 1146 (m),  
1121 (s), 1005 (s), 856 (m), 760 (m)

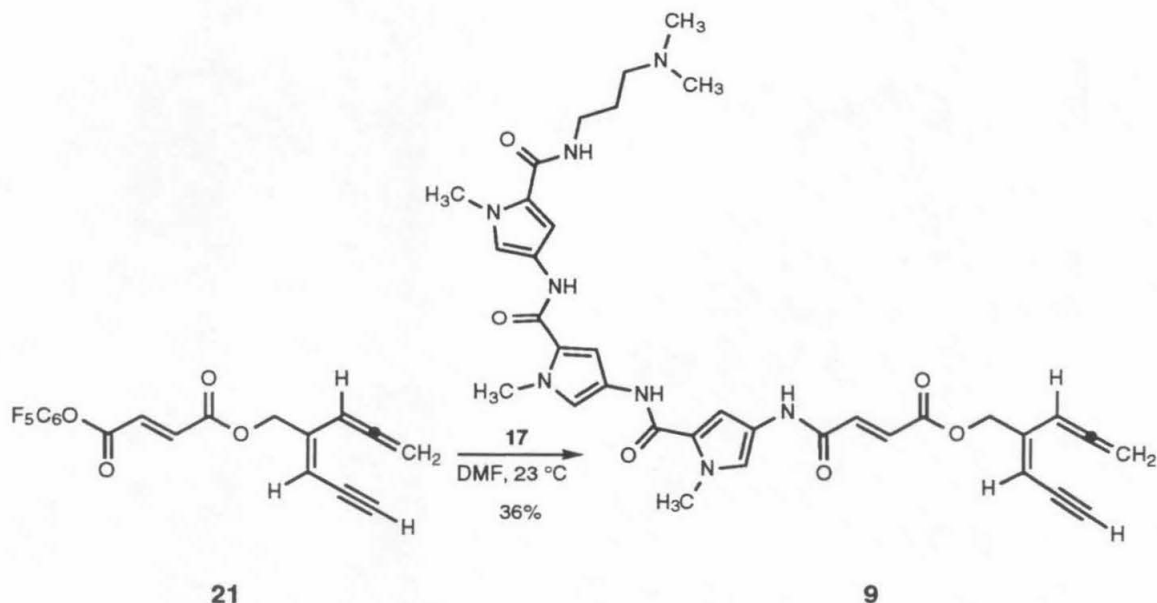
HRMS (FAB):

Calc'd for  $C_{18}H_9F_5O_4$   $[M]^-$ : 384.0421

Found: 384.0445

TLC (20% EtOAc in hexanes),  $R_f$ :

0.67



Palladium (10%) on activated carbon (11.6 mg) was added to a 100 mL Schlenk-type flask (the use of an oversized flask appears to be important for success in this reaction) containing a deoxygenated solution of 4-nitropyrrole-2-carboxamide **16** (33.0 mg, 66.3  $\mu\text{mol}$ , 1 equiv)<sup>17</sup> in methanol (8.0 mL), and the resultant suspension was deoxygenated. The reaction flask was then purged with hydrogen gas, and the reaction solution was stirred under 1 atm of hydrogen for 2.5 h at 23 °C. The reaction mixture was filtered through Celite, and the filtrate was concentrated. The residue was concentrated twice from dichloromethane (10 mL) and was then lyophilized from benzene (10 mL) to afford the 4-aminopyrrole-2-carboxamide **17** ( $R_f$  = 0.30, 3% ammonium hydroxide–methanol) as an air-sensitive yellow powder that was immediately coupled with the pentafluorophenyl ester **21**.

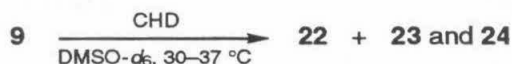
Pentafluorophenyl ester **21** (25.5 mg, 66.3  $\mu\text{mol}$ , 1.0 equiv) was added to a deoxygenated solution of the crude 4-aminopyrrole-2-carboxamide **17**, prepared above, in *N,N*-dimethylformamide (6.0 mL). The reaction mixture was observed to darken to a golden color. After being stirred for 1 h at 23 °C, the reaction mixture was poured into water (65 mL), and the product was extracted with dichloromethane (3  $\times$  60 mL). The combined organic layers were washed with water (2  $\times$  100 mL), were dried over sodium

sulfate, and were concentrated. The residue was purified by flash chromatography (1% ammonium hydroxide in 1:1 acetonitrile–methanol) wherein acetic acid (2–3 drops) was added to each fraction as it eluted. Fractions containing product **9** were pooled and concentrated, and the residue was lyophilized from dimethyl sulfoxide (2 mL) to afford the conjugate **9** as its acetate salt (yellow film, 17 mg, 36%).

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ),  $\delta$ : 10.66 (s, 1H,  $\text{CH=CHCONH}$ ), 9.99 (s, 1H,  $\text{NH}$ ), 9.90 (s, 1H,  $\text{NH}$ ), 8.07 (br s, 1H,  $\text{CONHCH}_2$ ), 7.34 (s, 1H, aromatic), 7.24 (s, 1H, aromatic), 7.19 (d, 1H,  $J = 14.6$  Hz,  $\text{CH=CH}$ ), 7.17 (s, 1H, aromatic), 7.03 (s, 1H, aromatic), 6.97 (s, 1H, aromatic), 6.81 (s, 1H, aromatic), 6.68 (d, 1H,  $J = 15.8$  Hz,  $\text{CH=CH}$ ), 6.41 (t, 1H,  $J = 7.0$  Hz,  $\text{HC=C=CH}_2$ ), 5.74 (s, 1H,  $\text{C=CHC}\equiv\text{C}$ ), 5.30 (d, 2H,  $J = 7.0$  Hz,  $\text{HC=C=CH}_2$ ), 4.77 (s, 2H,  $\text{CH}_2\text{OR}$ ), 4.48 (s, 1H,  $\text{C}\equiv\text{CH}$ ), 3.86 (s, 3H,  $\text{NCH}_3$ ), 3.83 (s, 3H,  $\text{NCH}_3$ ), 3.78 (s, 3H,  $\text{NCH}_3$ ), 3.17 (m, 2H,  $\text{CONHCH}_2$ ), 2.23 (t, 2H,  $J = 6.6$  Hz,  $\text{CH}_2\text{N}(\text{CH}_3)_2$ ), 2.12 (s, 6H,  $\text{N}(\text{CH}_3)_2$ ), 1.82 (s, 3H, acetate), 1.60 (m, 2H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ )

$^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ )  $\delta$ : 210.4 ( $\text{C=C=C}$ ), 172.5 ( $-\text{OCOCH}_3$ ), 164.5 ( $\text{RCO}_2\text{CH}_2\text{R}$ ), 161.2 ( $\text{CONH}$ ), 159.5 ( $\text{CONH}$ ), 158.4 ( $\text{CONH}$ ), 158.2 ( $\text{CONH}$ ), 141.2 ( $\text{HC}\equiv\text{CCH=C}$ ), 137.8 ( $\text{C(O)CH=CHC(O)}$ ), 127.7 ( $\text{C(O)CH=CHC(O)}$ ), 123.3, 123.0, 122.8, 122.1, 122.0, 121.3, 118.8, 118.4, 117.7,

|   |  |
|---|--|
|   | 107.5, 104.6 (aromatic and $\text{HC}\equiv\text{CCH}=\text{C}$ ), 104.0, 90.0 ( $\text{C}=\text{C}=\text{CH}_2$ ), 88.6 ( $\text{RC}\equiv\text{CH}$ ), 79.8 ( $\text{RC}\equiv\text{CH}$ ), 79.6 ( $\text{C}=\text{C}=\text{CH}_2$ ), 63.9 ( $\text{CH}_2\text{OR}$ ), 57.1 ( $\text{CONHCH}_2$ ), 45.1, 37.1, 36.2, 36.0, 35.9, 27.1 ( $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ ), 21.9 ( $^-\text{OCOCH}_3$ ) |
| FTIR (neat), $\text{cm}^{-1}$ :                                     | 3401 (br), 3284 (br), 2943 (m), 1931 (w), 1720 (m), 1641 (s), 1578 (s), 1555 (s), 1465 (m), 1435 (s), 1405 (s), 1349 (w), 1290 (m), 1263 (s), 1208 (m), 1165 (m), 1149 (m), 1106 (w), 1049 (w), 1020 (m), 1005 (m), 885 (w), 814 (w), 774 (m), 668 (w), 609 (w)  |
| HRMS (FAB):   | Calc'd for $\text{C}_{35}\text{H}_{40}\text{N}_8\text{O}_6$ $[\text{M} + \text{H}]^+$ : 669.3149<br>Found: 669.3142  |
| TLC (3% $\text{NH}_4\text{OH}$ in $\text{CH}_3\text{OH}$ ), $R_f$ : | 0.38   |



Thermal cyclization studies of conjugate **9** (3.0–3.8 mM) were conducted in dimethyl sulfoxide- $d_6$  solution containing 1,4-cyclohexadiene (CHD, 30–300 mM) in sealed NMR tubes. Each reaction solution was thoroughly deoxygenated by several freeze–pump–thaw cycles prior to flame-sealing under vacuum. Samples prepared for kinetics runs contained *N,N*-dimethylformamide (25 mM) as an internal standard and were analyzed periodically by  $^1\text{H}$  NMR, integrating against the formyl proton resonance. Thermolyses were conducted at temperatures from 30–37  $^\circ\text{C}$  in a regulated sand bath for a total reaction period of 85–90 h. Upon the completion of the reaction, the product solutions were analyzed by  $^1\text{H}$  NMR and by reverse-phase high-performance liquid chromatography (rp-HPLC). rp-HPLC was conducted using Vydac analytical (10  $\mu\text{m}$ ,  $0.46 \times 25$  cm, flow rate of 0.4 mL/min) or preparative (10  $\mu\text{m}$ ,  $2.2 \times 25$  cm, flow rate of 7.0 mL/min) reverse-phase C18 (201HS) columns, employing acetonitrile and aqueous ammonium acetate buffer solution (10 mM, pH 5.5) as eluent in a linear gradient of 30:70 to 60:40, respectively, over a 30 min period followed by isocratic elution (60:40). Cyclization product **22** was typically formed in 25% yield. Isomers **23** and **24** were also formed in 25% (combined) yield. Product **22** (retention time of 25 min) and the mixture of isomers **23** and **24** (inseparable, retention time of 37 min) were separated by HPLC and were characterized as follows.

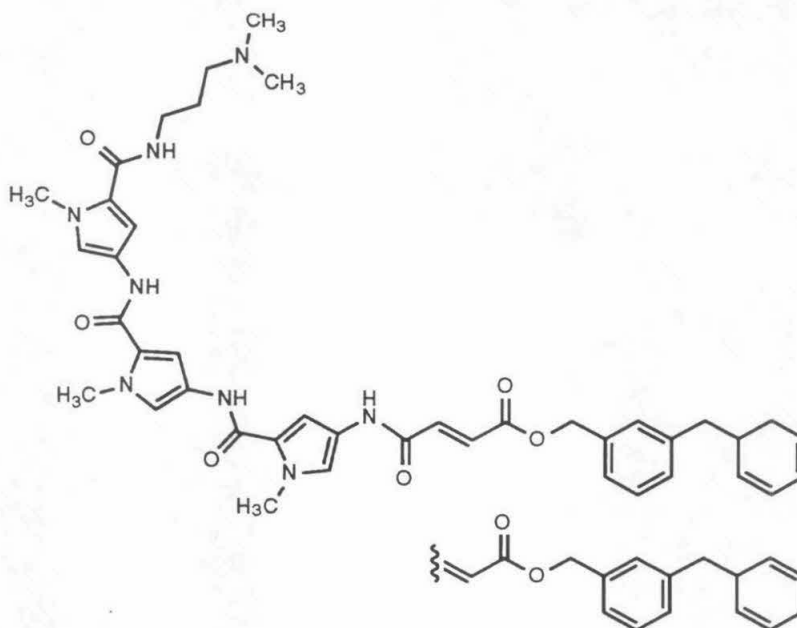


(m), 1437 (s), 1402 (s), 1349 (w), 1296 (w),  
1261 (m), 1208 (w), 1155 (w), 1102 (w)

HRMS (FAB):

Calc'd for  $C_{35}H_{43}N_8O_6$   $[M + H]^+$ : 671.3305

Found: 671.3297



**23 and 24**

Isomers **23** and **24**:

$^1H$  NMR (400 MHz, DMSO- $d_6$ ),  $\delta$ : 10.67 (s, 1H, CH=CHC(O)NH), 9.99 (s, 1H, NH), 9.89 (s, 1H, NH), 8.07 (br s, 1H, NHCH<sub>2</sub>), 7.33 (s, 1H, aromatic), 7.17–7.32 (5H, aromatic + CH=CH), 7.24 (s, 1H, aromatic), 7.17 (s, 1H, aromatic), 7.02 (s, 1H, aromatic), 6.96 (s, 1H, aromatic), 6.81 (s, 1H, aromatic), 6.70 (d, 1H,  $J$  = 15.0 Hz, CH=CH), 5.55–5.87 (m, cyclohexadienyl protons), 5.20 (s, 2H,

CH<sub>2</sub>OR), 3.85 (s, 3H, NCH<sub>3</sub>), 3.83 (s, 3H, NCH<sub>3</sub>), 3.78 (s, 3H, NCH<sub>3</sub>), 3.18 (m, 2H, NHCH<sub>2</sub>R), 2.65 (d, ArCH<sub>2</sub>CH), 2.22 (t, 2H,  $J = 7.0$  Hz, CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>), 2.12 (s, 6H, N(CH<sub>3</sub>)<sub>2</sub>), 1.74–1.76 (–OAc (buffer)), 1.59 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>)

FTIR (neat), cm<sup>-1</sup>:

3383 (br), 2954 (w), 2908 (s), 2837 (s), 1655 (w), 1631 (m), 1578 (s), 1561 (s), 1543 (m), 1525 (m), 1467 (w), 1402 (m), 1349 (w), 1249 (w), 1061 (br), 861 (m)

HRMS (FAB):

Calc'd for C<sub>41</sub>H<sub>49</sub>N<sub>8</sub>O<sub>6</sub> [M + H]<sup>+</sup>: 749.3775

Found: 749.3777

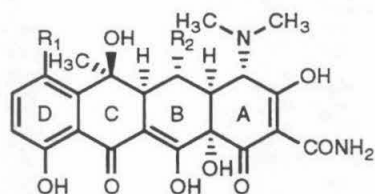


## **Chapter 2**

### **Studies Directed Toward the Total Synthesis of Tetracycline**

## Introduction

The tetracyclines were discovered 50 years ago as metabolites from assorted *Streptomyces* strains and proceeded to become some of the most useful broad-spectrum antibiotics on the market. The first tetracycline to be isolated was chlortetracycline **26** (trademarked Aureomycin),<sup>37</sup> followed shortly thereafter by oxytetracycline **27** (trademarked Terramycin).<sup>38</sup> Tetracycline itself (**28**) was first prepared chemically by the hydrogenolysis of chlortetracycline in 1953 and was subsequently isolated from the fermentation products of *Streptomyces aureofaciens*.<sup>39</sup>

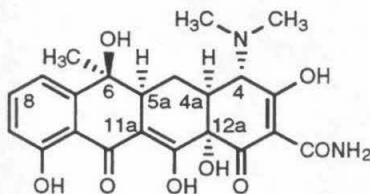


**26**  $R_1 = \text{Cl}, R_2 = \text{H}$

**27**  $R_1 = \text{H}, R_2 = \text{OH}$

**28**  $R_1 = \text{H}, R_2 = \text{H}$

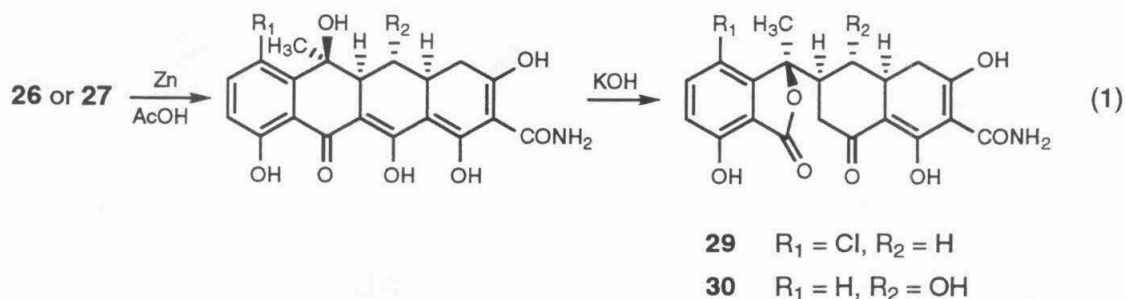
The tetracyclines are highly functionalized molecules, containing polar groups, acidic functionality, and as many as six stereogenic centers within an octahydronaphthacene core. They contain two distinct chromophoric regions which provide highly characteristic UV spectra.<sup>40</sup> These yellow crystalline compounds also fluoresce, especially when complexed with metal cations. Under mildly acidic conditions (pH ~2–6), epimerization at the C-4 position can occur; however, the natural  $\alpha$ -C-4 stereochemistry of tetracycline (see **28** below) can be re-established quantitatively by warming tetracycline mixtures in a basic medium containing a metal cation.<sup>41</sup> The binding of a metal cation such as calcium between



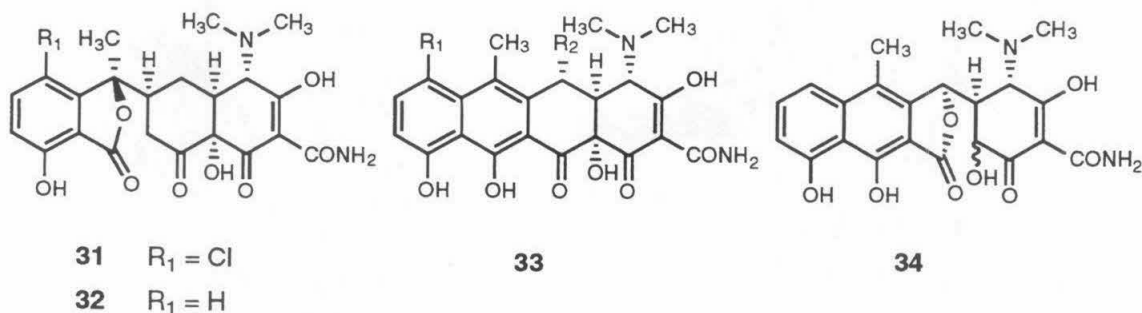
**28**

the C-4 amino group and the C-12a hydroxyl group is possible only when they are in a *cis* relationship.

The structures of chlortetracycline and oxytetracycline were elucidated in the early 1950s through extensive degradation studies.<sup>42-44</sup> This landmark effort was carried out almost exclusively by chemists at Pfizer Inc. in collaboration with R. B. Woodward and co-workers at Harvard University. Results from these degradation studies have influenced the efforts to develop a synthetic route to tetracycline described in this dissertation and are briefly mentioned here. Reduction of chlortetracycline or oxytetracycline with zinc in acetic acid gave rise to loss of the 4-dimethylamino and 12a-hydroxyl groups; alkali-induced rearrangement then provided the substituted phthalides **29** and **30**, respectively, by a retro-Dieckmann reaction (eq 1). Similarly, treatment of chlortetracycline or tetracycline with



dilute alkali led to their isomerization to form the products **31** and **32**, respectively. Under acidic conditions ( $\text{pH} \leq 2$ ) tetracyclines are dehydrated to form anhydrotetracyclines (**33**). The dehydration of oxytetracycline to give **33** ( $R_1 = \text{H}, R_2 = \text{OH}$ ) can then lead to its further degradation under basic conditions to provide the apoterramycins (**34**). These studies indicate the acute sensitivity toward both acid and base of the full tetracycline



system and suggest that planned syntheses should provide for its formation under mild conditions.

Several of the tetracyclines display antimicrobial activity effective against both gram-positive and gram-negative bacteria.<sup>45</sup> Most tetracyclines, including **28**, prevent bacterial growth through inhibition of protein synthesis, the result of specific binding of the drug to a ribosomal subunit in the cytoplasm. Some tetracyclines, however, do not directly inhibit bacterial protein synthesis, but rather appear to interfere with the bacterial cell membrane to cause cell lysis.<sup>46</sup> Tetracycline (**28**) once enjoyed common usage as a broad-spectrum antibiotic; however, the emergence of resistant bacterial strains has curtailed its use in the clinic.<sup>47</sup>

It has been determined from the study of numerous derivatives and degradation products of tetracycline that considerable structural modification of the non-chromophoric regions of rings B, C, and D can be performed without loss of antimicrobial activity. In fact, such changes have produced many new bioactive compounds.<sup>45,48,49</sup> A number of these tetracycline analogs have been prepared through chemical modification of the natural tetracyclines, although some have been prepared via laborious total syntheses (*vide infra*).

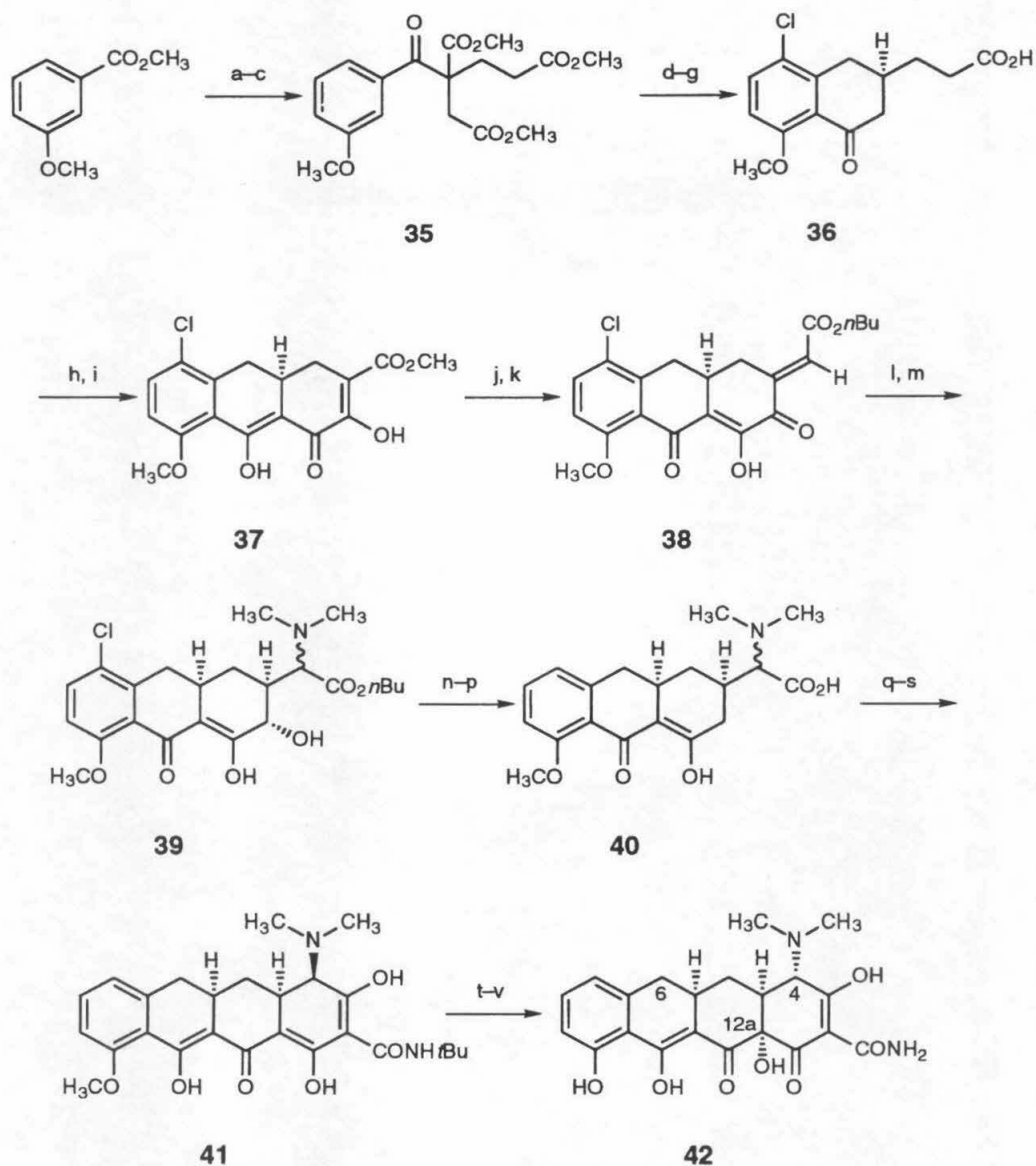
Despite all the synthetic and semi-synthetic studies of the tetracyclines, the parent tetracycline (**28**) has never been prepared through total chemical synthesis. One motivation for such an effort is this finding that chemical modification of tetracycline can overcome bacterial resistance. A concise and versatile laboratory synthesis of **28** would allow for the preparation of antibiotic candidates that are currently unavailable by semi-synthesis and might serve to revitalize interest in this family of antibiotics. This thesis describes efforts to accomplish this objective.

## Background

The first total synthesis of a member of the tetracycline class was described by Woodward and co-workers in 1962.<sup>50</sup> 6-Demethyl-6-deoxytetracycline **42**, the simplest

biologically active tetracycline which can be obtained by the hydrogenolysis of the natural product 6-demethyltetracycline,<sup>51</sup> was prepared in racemic form by the stepwise construction of rings D through A as shown in Scheme IV. Their synthesis is summarized as follows. Claisen condensation of methyl 3-methoxybenzoate with methyl acetate (NaH, DMF) and subsequent alkylation of the crude product with methyl chloroacetate gave an intermediate keto diester in 55% overall yield. Michael addition of this keto diester to methyl acrylate (Triton B, CH<sub>3</sub>OH) provided the keto triester **35** (88% crude yield). Decarboxylative hydrolysis of **35** (AcOH, H<sub>2</sub>SO<sub>4</sub>, H<sub>2</sub>O, 100 °C) followed by hydrogenation of the intermediate keto diacid (H<sub>2</sub>, Pd/C, AcOH, 200 psi) afforded a diacid in which the conjugated ketone had been deoxygenated. It should be noted that the ketone was removed merely to prepare the simple tetracycline initially targeted. Woodward and co-workers saw this group (which would become the C-6 position of **42**) as a way to introduce further functionality in future syntheses of the more complex tetracyclines containing the C-6 methyl and hydroxyl groups (such as **26–28**). *para*-Chlorination (Cl<sub>2</sub>, AcOH, 15 °C) of the aromatic ring of the diacid was carried out to block cyclization at this position in the next step. The C ring was then established by internal Friedel–Crafts acylation (liquid hydrogen fluoride, 15 °C) to give the tetralone **36** (19% yield from **35**). Conversion of the acid to the methyl ester (H<sub>2</sub>SO<sub>4</sub>, CH<sub>3</sub>OH, 66%) and subsequent Claisen/Dieckmann condensation of this product with dimethyl oxalate (NaH, DMF, CH<sub>3</sub>OH, 80→120 °C, 45%) provided the tricyclic compound **37**. The latter reaction required much experimentation in order to overcome the starting material's propensity to undergo an internal condensation. Ester hydrolysis and subsequent decarboxylation of **37** (AcOH, HCl, H<sub>2</sub>O, 100 °C, 73%) then provided a 1,2-dione that was condensed with *n*-butyl glyoxylate in the presence of magnesium methoxide (refluxing toluene, 52%) to give, as a single isomer, the ester **38**. Michael addition of dimethylamine to ester **38** (–10 °C) gave an amino ester adduct reversibly; direct reduction of this product with sodium borohydride (wet 1,2-dimethoxyethane, –70 °C) afforded the alcohol **39** in 52% yield.

## Scheme IV



Reagents and conditions: (a)  $\text{CH}_3\text{CO}_2\text{CH}_3$ , NaH, DMF; (b) NaH,  $\text{ClCH}_2\text{CO}_2\text{CH}_3$ , 55%; (c)  $\text{H}_2\text{C}=\text{CHCO}_2\text{CH}_3$ , Triton B,  $\text{CH}_3\text{OH}$ , 88%; (d) AcOH,  $\text{H}_2\text{SO}_4$ ,  $\text{H}_2\text{O}$ , 100 °C; (e)  $\text{H}_2$ , Pd/C, AcOH, 200 psi; (f)  $\text{Cl}_2$ , AcOH, 15 °C; (g) HF, 15 °C, 19% from 35; (h)  $\text{H}_2\text{SO}_4$ ,  $\text{CH}_3\text{OH}$ , 66%; (i) NaH, DMF,  $\text{CH}_3\text{O}_2\text{CCO}_2\text{CH}_3$ ,  $\text{CH}_3\text{OH}$ , 80→120 °C, 45%; (j) AcOH, HCl,  $\text{H}_2\text{O}$ , 100 °C, 73%; (k)  $n\text{BuO}_2\text{CCHO}$ ,  $\text{Mg}(\text{OCH}_3)_2$ ,  $\text{PhCH}_3$ , reflux, 52%; (l)  $\text{HN}(\text{CH}_3)_2$ , -10 °C; (m)  $\text{NaBH}_4$ ,  $\text{H}_2\text{O}$ , DME, -70 °C, 52% from 38; (n) *p*-TsOH,  $\text{PhCH}_3$ , reflux, 90%; (o) Zn,  $\text{HCO}_2\text{H}$ , 81%; (p)  $\text{H}_2$ , Pd/C,  $\text{Et}_3\text{N}$ , EtOH, 91%; (q)  $\text{ClCO}_2i\text{Pr}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CHCl}_3$ , 0 °C; (r) ( $\text{EtOMg}$ ,  $\text{EtO}_2\text{CCH}_2\text{CONH}i\text{Bu}$ ),  $\text{CH}_3\text{CN}$ ; (s) NaH, DMF, 23 °C;  $\text{CH}_3\text{OH}$ , 120 °C, 15% from 40; (t) 48%  $\text{HBr}/\text{H}_2\text{O}$ , 100 °C, 72%; (u)  $\text{O}_2$ ,  $\text{CeCl}_3$ ,  $\text{CH}_3\text{OH}$ , DMF, pH 10 buffer; (v)  $\text{CaCl}_2$ ,  $\text{HOCH}_2\text{CH}_2\text{NH}_2$  (pH 8.5), *n*BuOH,  $\text{H}_2\text{O}$ , reflux, 6.5%.

(equilibration in the dimethylamine addition reaction ensured that the side chain would be in the more stable equatorial position). Alcohol **39** then underwent lactonization (*p*-toluenesulfonic acid, refluxing toluene, 90%), reduction (Zn, HCO<sub>2</sub>H, 81%), and dechlorination (H<sub>2</sub>, Pd/C, Et<sub>3</sub>N, EtOH, 91%) to provide amino acid **40**. Formation of a mixed anhydride from **40** (ClCO<sub>2</sub>*i*Pr, Et<sub>3</sub>N, CHCl<sub>3</sub>, 0 °C) allowed for coupling with the ethoxymagnesio derivative of ethyl *N*-*t*-butylmalonamate (prepared by reaction of ethyl cyanoacetate with isobutylene in a sulfuric and acetic acid mixture) in acetonitrile. Finally, the closure of the A ring by Dieckmann condensation was effected in a capricious final step to provide the tetracyclic product **41** in 15% overall yield from **40** (NaH, DMF, 23 °C; CH<sub>3</sub>OH, 120 °C). Based upon inspection of models and by comparison with the degradation products of 6-demethyltetracycline, Woodward and co-workers proposed that the more stable orientation for the dimethylamino group would be as shown (β-epimer). Treatment of **41** under strongly acidic conditions (48% HBr, H<sub>2</sub>O, 100 °C, 72%) led to cleavage of the *t*-butylamide and methyl ether protective groups. Hydroxylation of the C-12a position using molecular oxygen (CeCl<sub>3</sub>, CH<sub>3</sub>OH, DMF, pH 10 buffer) and subsequent epimerization of the C-4 dimethylamino group in the presence of calcium chloride (pH 8.5 ethanolamine buffer, *n*-BuOH, H<sub>2</sub>O, reflux) provided the target compound **42** in 6.5% yield. Although a remarkable feat, their synthesis provided **42** in 22 steps with an overall yield of only ~0.003%.

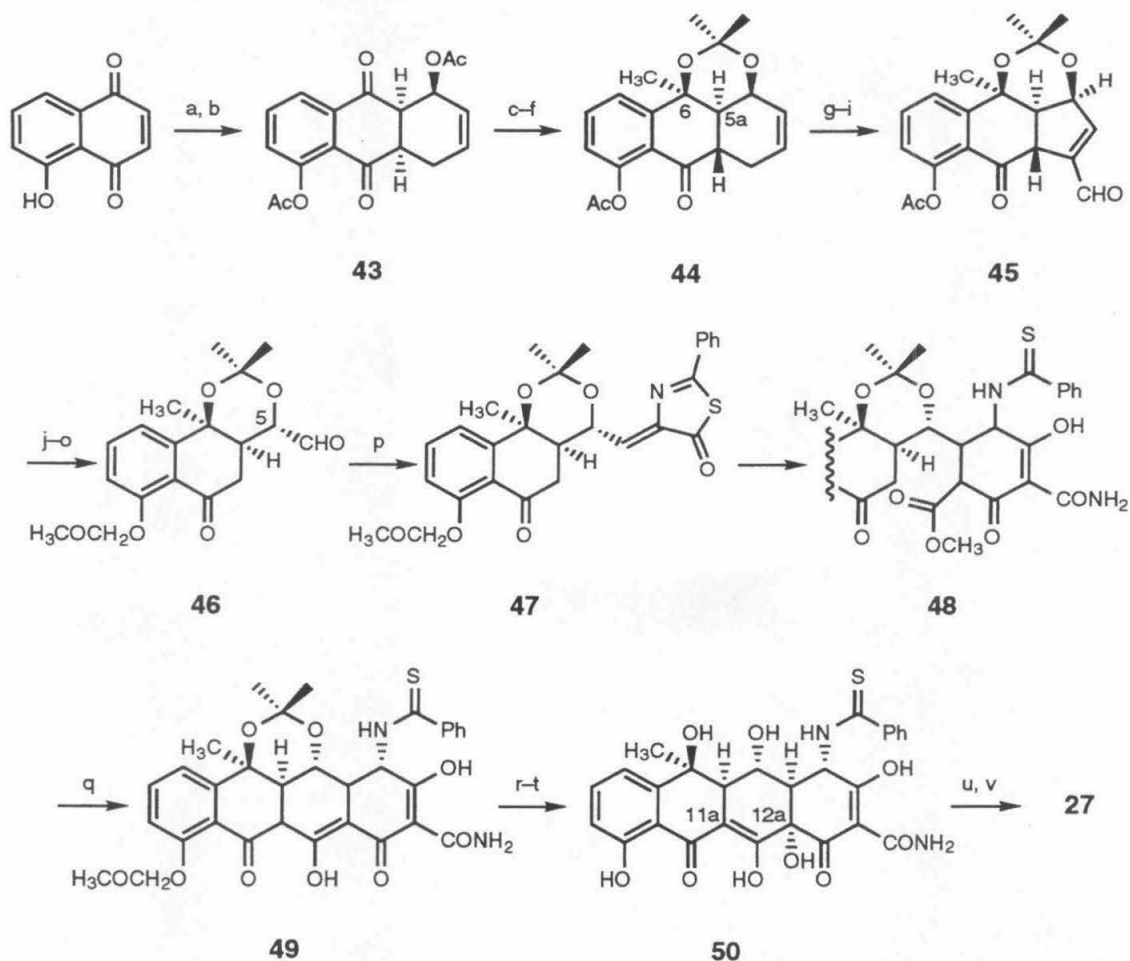
One of the most important aspects of the Woodward synthesis is the C-12a hydroxylation reaction. The oxygenation conditions utilized in the synthesis of **42** were based on the group's previous work with tetracycline analogs in which the use of molecular oxygen in the presence of a variety of metal ions was found to effect the desired transformation. However, this reaction, when conducted on the authentic substrate, provided the desired hydroxylation product in very low yields, albeit stereoselectively. Woodward proposed that this selectivity arose from the orientation of the dimethylamino group, which effectively blocked oxygenation on the β-face.

A different synthesis of ( $\pm$ )-6-demethyl-6-deoxytetracycline **42** was published shortly afterwards by Muxfeldt and co-workers.<sup>52</sup> Their approach to **42** was also designed for later adaptation to produce the more highly substituted and synthetically challenging tetracycline, oxytetracycline (**27**).<sup>53</sup> As established by degradation chemistry, the more functionalized tetracyclines are extremely sensitive to acid and base, and, as discussed above, the C-6 hydroxyl group is susceptible to dehydration under acidic conditions (see **33**). Under basic conditions a retro-Dieckmann reaction occurs to form apoterramycin (see **34**). Muxfeldt and co-workers circumvented these problems by protecting the three hydroxyl groups of **27** with base-stable protecting groups that could later be cleaved under mildly acidic conditions.

The Muxfeldt synthesis began with the protection of juglone as its acetate ( $\text{Ac}_2\text{O}$ , 83%) and subsequent Diels–Alder reaction of this product with 1-acetoxy-1,3-butadiene (refluxing benzene, 60%) to provide the *endo*-adduct **43** in racemic form (Scheme V). This reaction established what would become the C-6 and C-5a stereocenters. Stereoselective addition of methylmagnesium iodide (toluene,  $-70\text{ }^\circ\text{C}$ , 82%) to **43** was then followed by saponification and concomitant epimerization to give the *trans* ring fusion ( $\text{KOH}$ ,  $\text{H}_2\text{O}$ , 84%). Protection of the resulting 1,3-diol as its acetonide (acetone,  $\text{CuSO}_4$ , 84%) and the phenol as its acetate ester ( $\text{Ac}_2\text{O}$ ,  $\text{NaOAc}$ ,  $100\text{ }^\circ\text{C}$ , 95%) led to the tricyclic structure **44**. Dihydroxylation of **44** under standard conditions ( $\text{OsO}_4$ ,  $\text{KClO}_3$ , THF,  $\text{H}_2\text{O}$ ,  $50\text{ }^\circ\text{C}$ , 89%) provided a diol, which was cleaved to the dialdehyde with lead(IV) acetate (acetone,  $40\text{ }^\circ\text{C}$ ) followed by an intramolecular aldol dehydration reaction ( $\text{DABCO}$ , piperidine,  $\text{AcOH}$ , xylene, reflux) to provide the ring-contracted product **45** in 52% overall yield. Ozonolysis of **45** was followed by treatment with water to afford a dialdehyde in 68% yield. Cleavage of the extraneous carbonyl group and hydrolysis of the phenyl ester was brought about under basic conditions ( $\text{Na}_2\text{CO}_3$ ,  $\text{CH}_2\text{Cl}_2$ , 85%) to give a mixture of aldehydes. This mixture was then submitted to the following series of reactions: enamine formation with piperidine (refluxing benzene, 91%), protection of the phenol ( $\text{NaH}$ , THF,



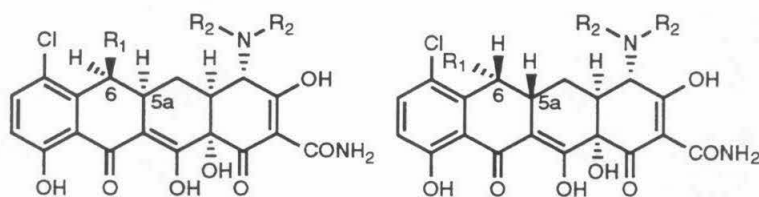
## Scheme V



Reagents and conditions: (a)  $\text{Ac}_2\text{O}$ , 83%; (b) 1-acetoxy-1,3-butadiene, PhH, reflux, 60%; (c)  $\text{CH}_3\text{MgI}$ ,  $\text{PhCH}_3$ ,  $-70^\circ\text{C}$ , 82%; (d)  $\text{KOH}$ ,  $\text{H}_2\text{O}$ , 84%; (e) acetone,  $\text{CuSO}_4$ , 84%; (f)  $\text{Ac}_2\text{O}$ ,  $\text{NaOAc}$ ,  $100^\circ\text{C}$ , 95%; (g)  $\text{OsO}_4$ ,  $\text{KClO}_3$ , THF,  $\text{H}_2\text{O}$ ,  $50^\circ\text{C}$ , 89%; (h)  $\text{Pb}(\text{OAc})_4$ , acetone,  $40^\circ\text{C}$ ; (i) DABCO, piperidine, AcOH, xylene, reflux, 52%; (j)  $\text{O}_3$ ,  $\text{CHCl}_3$ ,  $-50^\circ\text{C}$ ; (k)  $\text{H}_2\text{O}$ , 68%; (l)  $\text{Na}_2\text{CO}_3$ ,  $\text{CH}_2\text{Cl}_2$ , 85%; (m) piperidine, PhH, reflux, 91%; (n)  $\text{NaH}$ , THF,  $0^\circ\text{C}$ ;  $\text{ClCH}_2\text{OCH}_3$ ,  $23^\circ\text{C}$ , 90%; (o) deactivated silica gel, 70–80%; (p) 2-phenylthiazolin-5-one, basic lead acetate, THF,  $20^\circ\text{C}$ , 70%; (q) (methyl 3-oxoglutaramate,  $n\text{BuLi}$ ), THF,  $-78 \rightarrow 25^\circ\text{C}$ ;  $\text{LiOtBu}$ , reflux, 27%; (r) AcOH,  $\text{H}_2\text{O}$ , reflux, 90%; (s)  $\text{O}_2$ ,  $\text{NaH}$ ,  $\text{P}(\text{OEt})_3$ , THF, DMF,  $\text{H}_2\text{O}$ ; (t)  $\text{HCl}$ ,  $\text{CH}_3\text{OH}$ , 47%; (u)  $\text{CH}_3\text{I}$ , THF;  $\text{HCl}$ ,  $\text{H}_2\text{O}$ ; (v) dimethyl sulfate, DIPEA, THF, EtOH, 23%.

0 °C, chloromethyl methyl ether, 23 °C, 90%), and enamine cleavage with moist silica gel to give a solution of the aldehyde **46** in crude form. The latter product possessed the desired C-5 stereochemistry and was one of the key intermediates in Muxfeldt's strategy, embodying the left-hand half of the target tetracycline. The remaining two key components in the Muxfeldt synthesis were added sequentially in the next two steps. Thus, aldehyde **46** was condensed with 2-phenylthiazolin-5-one in the presence of basic lead acetate<sup>54</sup> to provide thiazolone **47** (70%). Then, in a truly remarkable reaction, three C–C bonds were formed to complete the synthesis of the tetracyclic framework. Thus, reaction of **47** with the lithium salt of methyl 3-oxoglutaramate (*n*-BuLi, –78→25 °C) effected closure of the A ring as shown in the partial structure **48**. Further addition of base (LiOt-Bu) and heating of the reaction mixture to reflux provided, after separation of the diastereomers by crystallization, the tetracyclic compound **49** in 27% yield. Deprotection of the aromatic ether (AcOH, H<sub>2</sub>O, reflux, 90%) preceded the critical C-12a hydroxylation reaction. Muxfeldt and co-workers conducted the latter transformation using gaseous oxygen in the presence of triethylphosphite and sodium hydride (THF, DMF, H<sub>2</sub>O). The crude C-12a-hydroxylated product was formed in ~52% yield along with the C-11a-hydroxylated product (~14% yield). This crude mixture was treated with acid (HCl, CH<sub>3</sub>OH) to afford the tetracycline **50** in 47% yield. Even with the C-4 dimethylamino group existing as the desired  $\alpha$ -epimer, the C-12a hydroxylation appeared to take place largely with the desired  $\alpha$ -stereochemistry. Methylation and hydrolysis of the thioamide protecting group (CH<sub>3</sub>I, THF; HCl, H<sub>2</sub>O) liberated the amino group, which was methylated under standard conditions (dimethyl sulfate, DIPEA, THF, EtOH) to provide oxytetracycline **27** in 23% yield. In this manner, oxytetracycline **27** was synthesized in 22 linear steps in an overall yield of ~0.1%. The key feature of this work is that three key pieces are utilized to quickly assemble the tetracycline core (rings A and B). Although this series of reactions is not stereoselective, the desired diastereomer is readily isolated by recrystallization or column chromatography.

Muxfeldt's synthetic route allowed for the first time the preparation and isolation of various tetracyclines with only minor changes to the original plan. In addition to the synthesis of ( $\pm$ )-6-demethyl-6-deoxytetracycline **42** and ( $\pm$ )-oxytetracycline **27**, Muxfeldt and co-workers utilized their synthetic strategy for the first and only synthesis of ( $\pm$ )-anhydroaureomycin<sup>55</sup> (and, by extension, Aureomycin **26**, based on the procedure by Scott and co-workers).<sup>56</sup> Moreover, their strategy was reportedly used by other workers to prepare tetracycline analogs. For example, a group at Hoechst AG prepared and studied the C-5a- and C-6-epimeric series of 7-chloro-6-deoxytetracycline in addition to C-5a-epi-7-chloro-6-demethyl-6-deoxytetracycline, as shown in structures **51** and **52**.<sup>57</sup> Tetracyclines containing a truncated B ring, the ( $\pm$ )-B-nortetracyclines (**53**), were also



**51**  $R_1 = H, R_2 = H$

$R_1 = CH_3, R_2 = H$

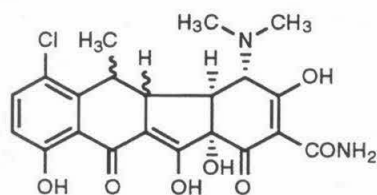
$R_1 = H, R_2 = CH_3$

$R_1 = CH_3, R_2 = CH_3$

**52**  $R_1 = H, R_2 = H$

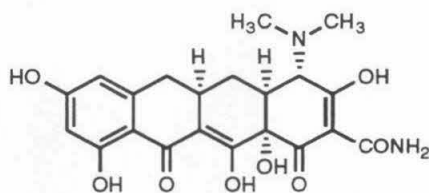
$R_1 = CH_3, R_2 = H$

$R_1 = H, R_2 = CH_2CH_3$

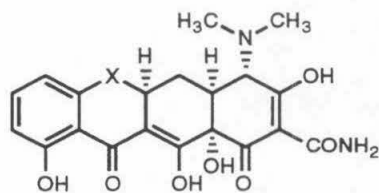


**53**

prepared by the Muxfeldt route.<sup>49</sup> One of the few examples of the introduction of functionality at the C-8 position was provided in the synthesis of racemic 8-hydroxy-6-demethyl-6-deoxytetracycline **54**.<sup>58</sup> Finally, the interesting and highly active analogs ( $\pm$ )-6-thiatetracycline (**55**,  $X = S$ )<sup>59</sup> and ( $\pm$ )-6-oxatetracycline (**55**,  $X = O$ )<sup>48</sup> were synthesized using the Muxfeldt strategy.

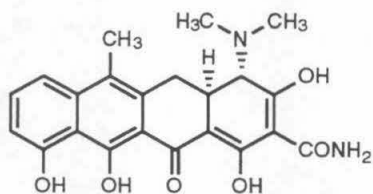


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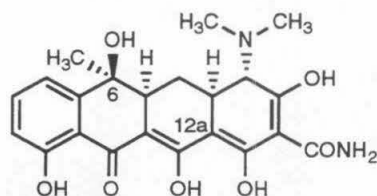


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There are also reported syntheses of 12a-deoxyanhydrotetracycline (**56**)<sup>60,61</sup> which, when combined with work by Wasserman and co-workers describing the synthesis of **28** from anhydrotetracycline **33** ( $R_1 = H$ ,  $R_2 = H$ ),<sup>62</sup> would constitute formal syntheses of tetracycline, provided that the single report of selective 12a-hydroxylation of **56** ( $O_2$ ,  $PtO_2$ ,  $Et_3N$ , THF, 20 °C)<sup>63</sup> can be verified. Similarly, 12a-deoxytetracycline (**57**) has been utilized as a synthetic intermediate. There are a number of methods that have been used to bring about the C-12a hydroxylation of **57** or its C-4 epimer, such as through the use of perbenzoic acid,<sup>64</sup> sodium nitrite,<sup>65</sup> a prehydrogenated platinum oxide catalyst with oxygen,<sup>66</sup> or a microbiological process,<sup>67</sup> although these generally proceed in low yield. Recently, however, Stork and co-workers reported that they were unable to reproduce the C-12a hydroxylation reactions described by Holmlund<sup>65</sup> or Muxfeldt<sup>66</sup> to transform **57** into tetracycline (*vide infra*). Similarly, the oxygenation procedure developed by Woodward



56



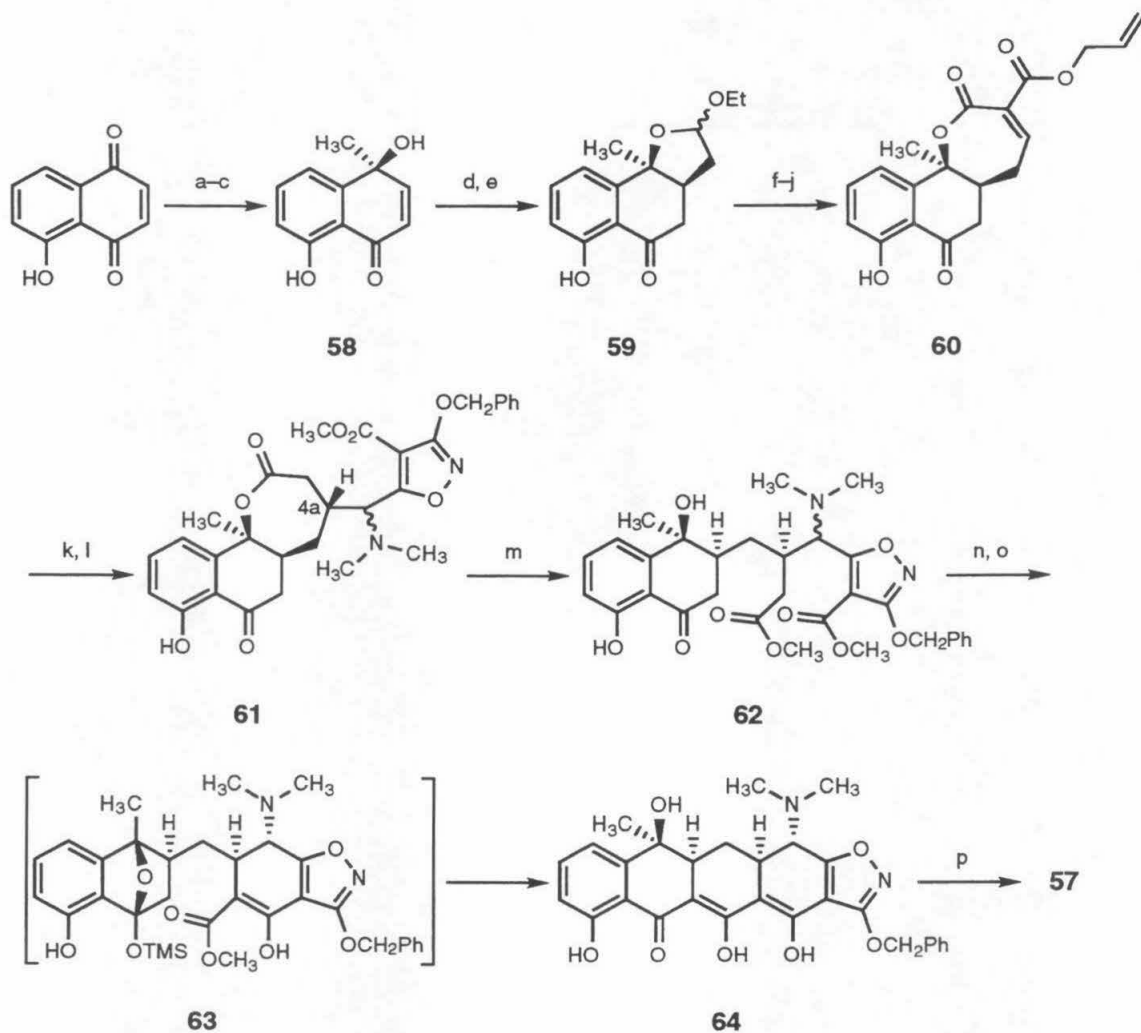
57

(cerous chloride, oxygen, pH 10 buffer)<sup>50c</sup> was also not successful in the Stork efforts. It should be noted that the Woodward and Muxfeldt (oxygen, triethylphosphite, sodium hydride)<sup>53</sup> oxygenation methods were originally used to hydroxylate the C-12a position of substrates with no C-6 hydroxyl group, or with a protected C-6 hydroxyl group. Even then, the reported yields for these procedures were low (<50%), and optimization of the

reaction conditions was typically necessary for each new substrate. Thus, it is clear that the incorporation of the C-12a hydroxyl group was, and remains, the challenging problem in the synthesis of tetracycline.

Recently, Stork and co-workers reported the first stereospecific total synthesis of a tetracycline, ( $\pm$ )-12a-deoxytetracycline **57** (Scheme VI).<sup>68</sup> Their efficient and high-yielding synthesis is outlined below. The double bond of 5-hydroxy-1,4-naphthoquinone was protected as a Diels–Alder adduct (cyclopentadiene,  $\text{CHCl}_3$ , 100%) such that only 1,2-addition to the carbonyl group could take place with methylmagnesium bromide (THF,  $-78 \rightarrow 23$  °C, 78%). Deprotection of the intermediate alcohol via a retro Diels–Alder reaction (*p*-xylene, heat, 100%) then provided the racemic alcohol **58**. Reaction of **58** with the bromine adduct of ethyl vinyl ether (*N,N*-dimethylaniline,  $\text{CH}_2\text{Cl}_2$ , heat, 98%), and subsequent radical cyclization of the intermediate haloacetal with tributyltin hydride (AIBN, PhH, heat, 90%) afforded the *cis*-fused acetal **59**. Protection of the masked aldehyde with 1,3-propane dithiol ( $\text{BF}_3 \cdot \text{OEt}_2$ ,  $\text{CH}_2\text{Cl}_2$ , 0 °C, 88%), esterification of the tertiary alcohol with a mixed anhydride formed from allyl malonate (TFAA, DME, 92%), cleavage of the dithiane by transacetalization ( $\text{PhI}(\text{OCOCF}_3)_2$ ,  $\text{CH}_3\text{OH}$ ,  $\text{CH}_2\text{Cl}_2$ , 92%; 5% aq. HCl, THF), and intramolecular condensation of the malonate ester with the resultant aldehyde (piperidine, AcOH, PhH,  $0 \rightarrow 23$  °C, 97%) provided the lactone **60**. This tricyclic lactone (**60**) was then used to set the C-4a stereocenter via a stereoselective Michael addition. Deprotonation of methyl 3-benzyloxy-5-dimethylaminomethyl-4-isoxazolecarboxylate with sodium bis(trimethylsilyl)amide and reaction of the anion with lactone **60** (THF,  $-78 \rightarrow -50$  °C) gave an intermediate addition product which then underwent removal of the allyl ester group ( $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{PPh}_3$ , ethylhexanoic acid, EtOAc,  $\text{CH}_2\text{Cl}_2$ , 95%) to provide intermediate **61**. Cleavage of the lactone within **61** with tributyltin methoxide ( $\text{PhCH}_3$ , 60 °C) afforded the cyclization precursor **62** in 97% yield. Based on their previous difficulties with forming the A ring last, it was crucial to the success of the synthesis that cyclization to form ring A occur prior to that of ring B. Thus,

## Scheme VI



Reagents and conditions: (a) cyclopentadiene,  $\text{CHCl}_3$ , 100%; (b)  $\text{CH}_3\text{MgBr}$ , THF,  $-78 \rightarrow 23^\circ\text{C}$ , 78%; (c) *p*-xylene, heat, 100%; (d)  $\text{EtOCHBrCH}_2\text{Br}$ , *N,N*-dimethylaniline,  $\text{CH}_2\text{Cl}_2$ , heat, 98%; (e)  $n\text{Bu}_3\text{SnH}$ , AIBN, PhH, heat, 90%; (f) 1,3-propanedithiol,  $\text{BF}_3 \cdot \text{OEt}_2$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ , 88%; (g)  $(\text{HO}_2\text{CCH}_2\text{CO}_2\text{CH}_2\text{CH}=\text{CH}_2)$ , TFAA, DME, 92%; (h)  $\text{PhI}(\text{OCOCF}_3)_2$ ,  $\text{CH}_2\text{Cl}_2$ ,  $\text{CH}_3\text{OH}$ , 92%; (i) 5%  $\text{HCl}$ , THF; (j) piperidine, AcOH, 4Å molecular sieves, PhH,  $0 \rightarrow 23^\circ\text{C}$ , 97%; (k) (NaHMDS, methyl 3-benzyloxy-5-dimethylaminomethyl-4-isoxazolecarboxylate), THF,  $-78 \rightarrow -50^\circ\text{C}$ ; (l)  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{PPh}_3$ , ethylhexanoic acid, 4Å molecular sieves, EtOAc,  $\text{CH}_2\text{Cl}_2$ , 95%; (m)  $\text{Bu}_3\text{SnOCH}_3$ , PhCH<sub>3</sub>,  $60^\circ\text{C}$ , 97%; (n) TMSCN, KCN, 18-crown-6,  $\text{CH}_2\text{Cl}_2$ ; (o) KH, THF,  $-78 \rightarrow 0^\circ\text{C}$ ;  $23 \rightarrow 50^\circ\text{C}$ , 59%; (p)  $\text{H}_2$ , Pd black, THF,  $\text{CH}_3\text{OH}$ , 94%.

the ketone in the C ring of **62** was protected as the trimethylsilyloxy ketal (TMSCN, KCN, 18-crown-6,  $\text{CH}_2\text{Cl}_2$ ), and the resultant intermediate was treated with base (KH, THF,  $-78 \rightarrow 0$  °C) to effect closure of the A ring, presumably via the intermediate **63**. The reaction mixture was then warmed to 50 °C to effect the second ring cyclization upon in situ cleavage of the trimethylsilyloxy ketal of ring C to provide the tetracyclic product **64** (59%). Hydrogenolysis of the isoxazole (Pd black,  $\text{H}_2$ , THF,  $\text{CH}_3\text{OH}$ , 94%) then gave the target substrate **57** in an impressive 25% yield over the 16 linear steps.

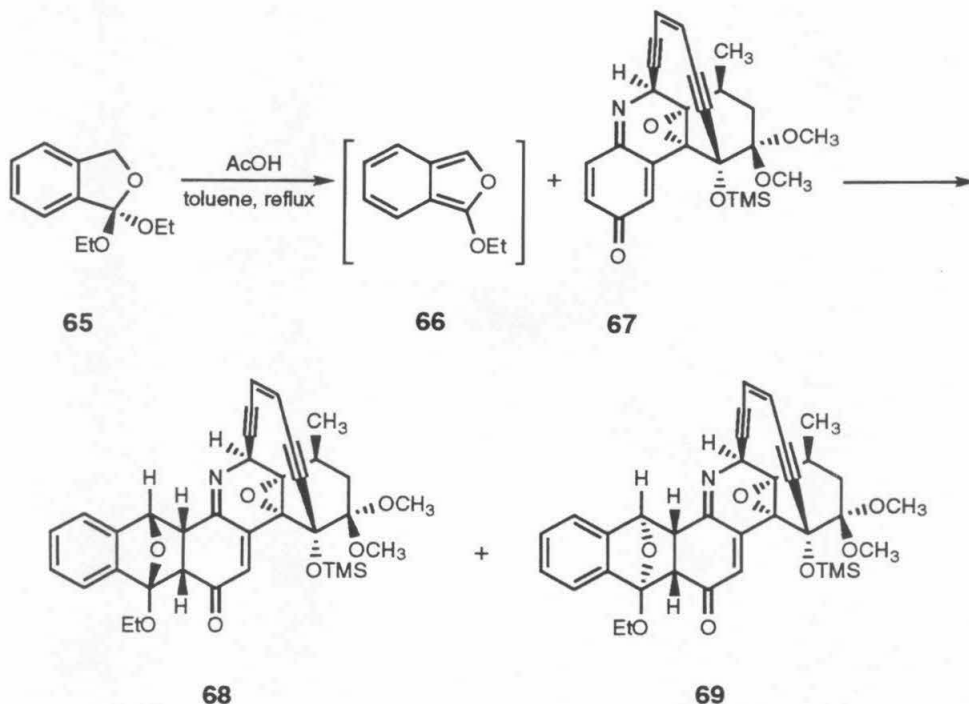
Several features of the Stork synthesis are noteworthy. The fact that this synthesis is highly stereoselective greatly simplifies product purification. All subsequent stereochemistry was dependent on the initial stereocenter within the early intermediate **58**. Thus, resolution of this material would permit the isolation of **57** in optically-active form. Another significant highlight is the clever way in which the sensitive functionality of the A ring is protected. The isoxazole ring system is stable to the various reaction conditions and is unmasked at the appropriate juncture to form the desired  $\beta$ -keto amide through a simple hydrogenation reaction. The transformation of **57** to tetracycline by hydroxylation of the C-12a position should have been viable using one of the many published hydroxylation methods described above. Unfortunately, Stork and co-workers have been unable to duplicate *any* of the C-12a hydroxylation methods for the purpose of synthesizing tetracycline.<sup>68</sup> To date, this C-12a hydroxylation reaction remains the key unsolved problem in the synthesis of fully functionalized tetracycline.

## Retrosynthetic Plan

Structure-activity relationship studies have determined that substitution along the C and D rings of tetracycline produces novel, active antibiotic substances, while substitution along the A and B rings produces primarily inactive compounds.<sup>48,69,70</sup> The goal of our research program was to provide a concise, enantioselective synthesis of the tetracyclines that would not only provide the first total synthesis of tetracycline but would also allow for

the preparation of a wide variety of analogs to aid in the discovery of new compounds with potentially improved pharmacological profiles.

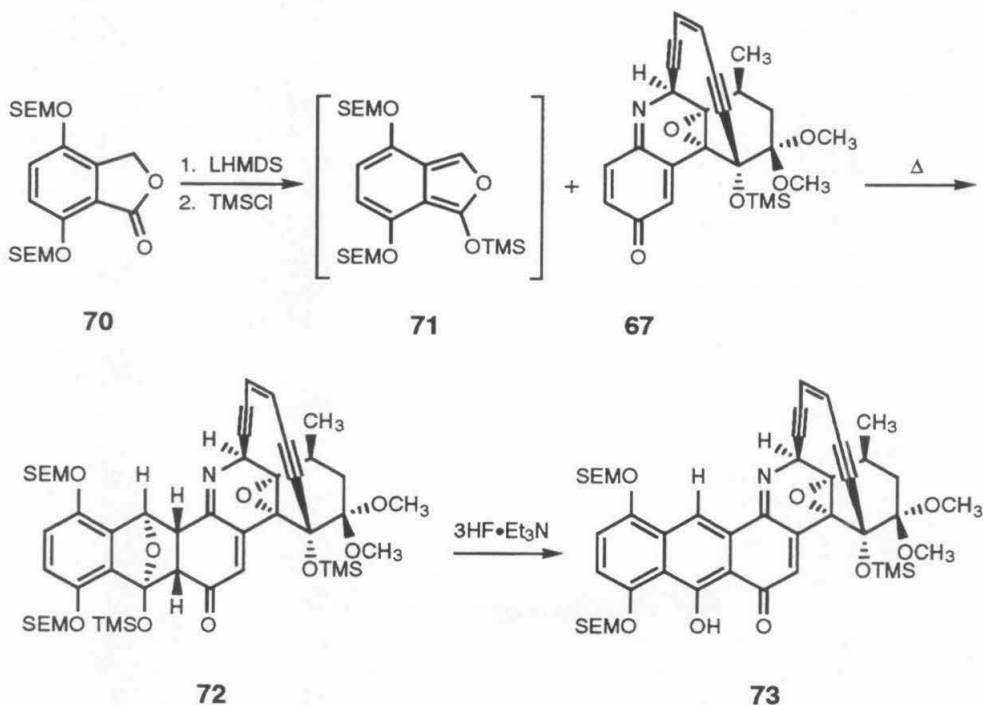
In studies leading to the total synthesis of (+)-dynamycin A, Myers and co-workers assembled the tricyclic anthraquinone core of the molecule by an isobenzofuran Diels–Alder cycloaddition,<sup>28</sup> an approach originally used by Kende and co-workers in synthetic studies toward the anthracycline antibiotics.<sup>71</sup> The isobenzofuran diene components utilized in the dynamycin studies were synthesized by two different methods,<sup>72</sup> the first method making use of 1,1-diethoxyphthalan **65** as an isobenzofuran precursor.<sup>73</sup> Heating a solution of **65** (5 equiv) and quinone imine **67** in toluene containing acetic acid (0.2 equiv) at reflux afforded the Diels–Alder adducts **68** and **69** in a combined yield of 56%. Adducts **68** and **69** were formed as a 1:1 mixture of *endo* and *exo* Diels–Alder products where both compounds were believed to arise from diene attack on the less hindered  $\alpha$ -face of the dienophile.



For the synthesis of the more highly oxygenated anthraquinones in the dynamycin system, a second method of isobenzofuran generation involving a deprotonation-silylation



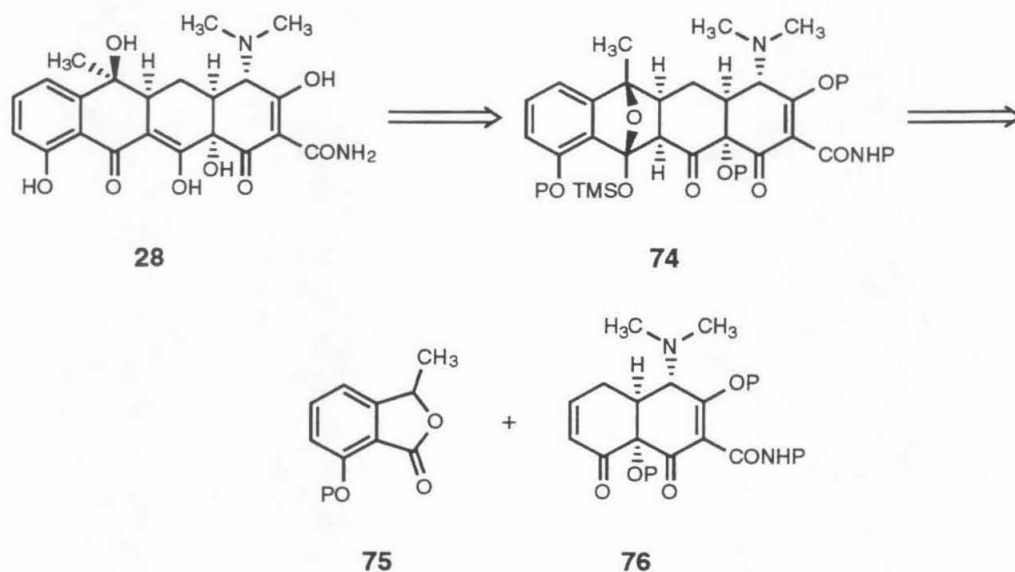
sequence was utilized.<sup>74</sup> Treatment of the phthalide **70** with lithium bis(trimethylsilyl)amide (THF,  $-78\text{ }^{\circ}\text{C}$ ) and subsequent trapping of the anion with chlorotrimethylsilane presumably formed the *O*-trimethylsilyloxy isobenzofuran **71**. Further reaction with the quinone imine **67** at ca.  $65\text{ }^{\circ}\text{C}$  provided exclusively the *exo* Diels–Alder adduct **72** in 34% yield. The additional steric hindrance of the isobenzofuran **71** was believed to prevent an *endo*-selective Diels–Alder cycloaddition. Cleavage of the trimethylsilyloxy ketal of **72** with triethylamine trihydrofluoride ( $\text{CH}_3\text{CN}$ ,  $23\text{ }^{\circ}\text{C}$ ) then afforded the naphthalenol **73** in 44% yield.



The application of the isobenzofuran Diels–Alder strategy to the synthesis of tetracycline would seem an almost ideal match based on the functionality present within the left-hand portion of the natural product. The use of this cycloaddition to assemble the two halves of tetracycline would provide a highly convergent and stereoselective path to the target, readily providing the  $\beta$ -diketone functionality of the BCD ring chromophore and potentially establishing two of five stereogenic centers in one reaction (Scheme VII, P = protecting group). The intermediate **74**, for example, contains the full retron for an

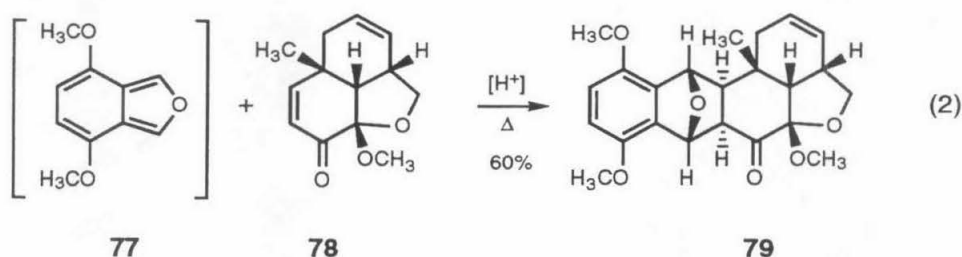
isobenzofuran Diels–Alder transform leading to its assembly from the phthalide **75** and the enone **76**. The synthesis of the isobenzofuran precursor (**75**) would follow established methodology for the synthesis of phthalides<sup>75</sup> and should readily accommodate a wide range of functionality on the aromatic ring as desired for new tetracycline antibiotic candidates. The synthesis of the right-hand half (**76**) is much less straightforward and is the most difficult part of this retrosynthetic scheme. Intermediate **76** comprises three stereogenic centers and much of the polar and reactive functionality of the parent tetracycline. Structure-activity relationships, discussed above, suggest that the right-hand precursor of tetracycline would not require the flexibility for analog preparation that is desirable within the left-hand precursor.

### Scheme VII



The feasibility of this retrosynthetic plan, however, depends upon one very important question: can the isobenzofuran Diels–Alder reaction be used to assemble the two halves of tetracycline with the requisite stereochemistry? To be useful, the isobenzofuran Diels–Alder cycloaddition must occur with *exo* and dienophile-facial

selectivity. As observed in the dynemicin synthetic studies discussed above, the stereochemistry of the isobenzofuran Diels–Alder reaction is very sensitive to changes in the substrate structures.<sup>76</sup> The use of a 4,7-disubstituted isobenzofuran in conjunction with a bulky tricyclic dienophile appears to favor an *exo*-selective Diels–Alder reaction, a conclusion further supported by the work of Rodrigo and co-workers in which the *exo* Diels–Alder adduct **79** was formed exclusively from the proposed isobenzofuran **77** and the enone **78** (eq 2).<sup>77</sup> However, as stated previously, this conclusion must await experimental proof in studies with the actual right-hand half of tetracycline. Minor changes in either substrate should prove beneficial towards tuning the Diels–Alder reaction to the desired outcome. In terms of the facial selectivity of the Diels–Alder reaction, it is hoped that a bulky protecting group for the  $\alpha$ -hydroxyl group within dienophile **76** can be used to block attack of the isobenzofuran from the  $\alpha$ -face of the dienophile. Chelation of a Lewis acid to the 1,3-dicarbonyl group of dienophile **76** may provide an additional site for controlling the selectivity of or enhancing the reactivity of the Diels–Alder reaction.



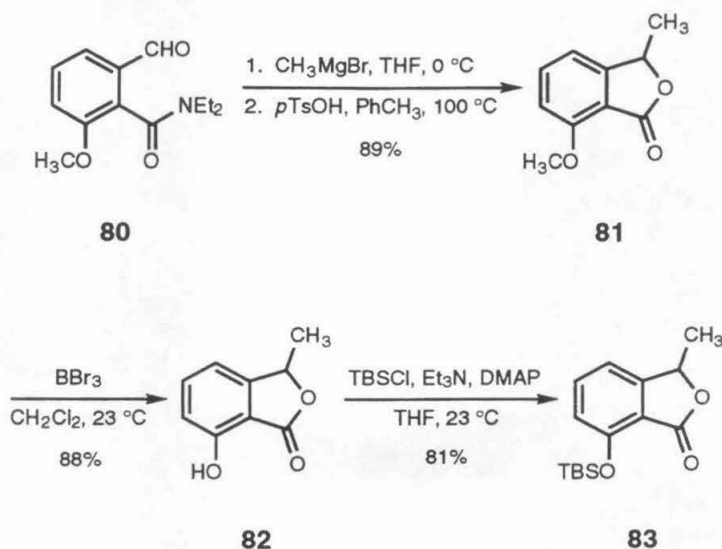
### Model Studies Relevant to the Isobenzofuran Diels–Alder Reaction

Although the issue of stereochemistry in the isobenzofuran Diels–Alder reaction was postponed pending completion of a fully functionalized right-hand half, the inherent reactivity of the proposed dienophile **76** was examined briefly in model studies. Retrosynthetic analysis had provided an enone as the right-hand target, a less electron-deficient dienophile than the benzyne, benzoquinones, and quinone imines commonly utilized in this reaction. In fact, the example shown in eq 2 is the only published example

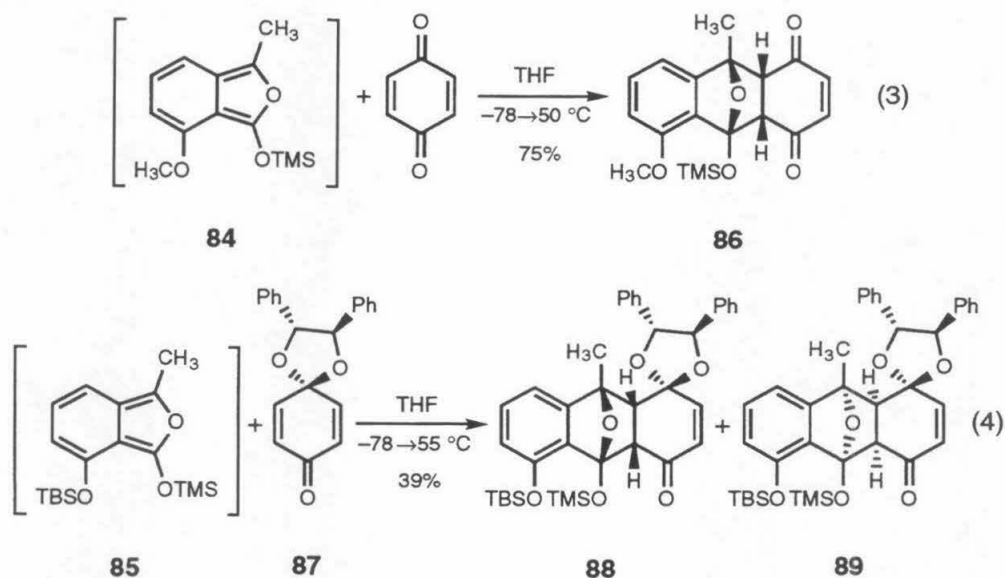
of an isobenzofuran Diels–Alder reaction with an enone as dienophile. This reaction is not directly applicable to the proposed system, however, because it takes place under conditions that are not compatible with 1,3-disubstituted isobenzofurans, which are unstable at room temperature.<sup>78</sup> Accordingly, the goal became to demonstrate that an *O*-trimethylsilyloxy isobenzofuran would react with an enone as dienophile under conditions compatible with the unstable isobenzofuran.

The synthesis of the isobenzofuran precursor for the left-hand half of tetracycline proceeded readily following the work of Snieckus and co-workers (Scheme VIII).<sup>75</sup> Treatment of aldehyde **80**, prepared from *o*-anisic acid, with methylmagnesium bromide (2.1 equiv) in tetrahydrofuran at 0 °C followed by cyclization of the secondary alcohol with *p*-toluenesulfonic acid monohydrate (1.1 equiv) in hot toluene (100 °C) afforded phthalide **81** in 89% yield. Demethylation of phthalide **81** with boron tribromide (2.4 equiv) in dichloromethane (−78→23 °C) produced 7-hydroxy-3-methylphthalide **82** in 88% yield. Protection of **82** as its *tert*-butyldimethylsilyl ether using TBSCl (3.0 equiv), triethylamine (4.0 equiv), and DMAP (0.1 equiv) in THF gave phthalide **83** (81%).

Scheme VIII

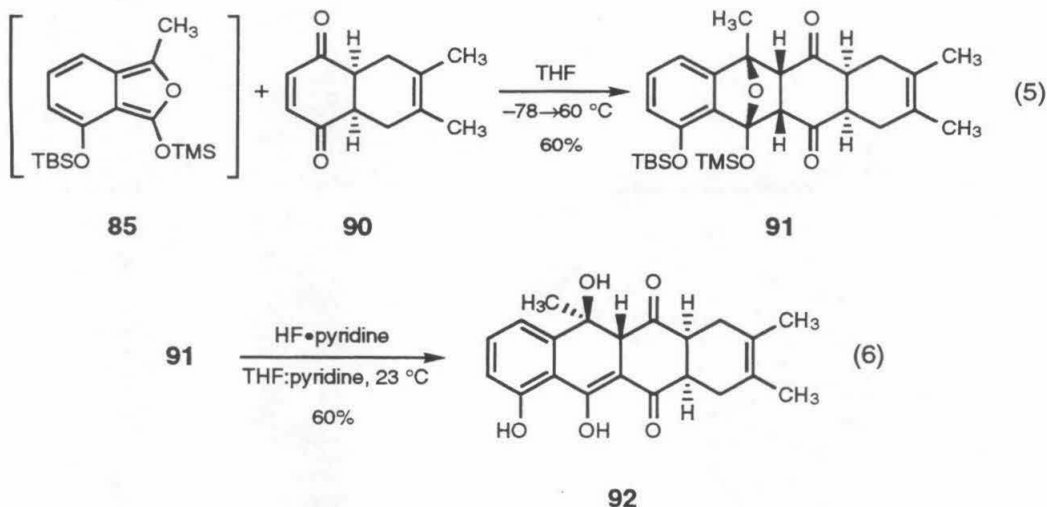


To accommodate functionalization on the phthalide, generation of the isobenzofuran through a deprotonation-silylation sequence was planned.<sup>74</sup> The proposed isobenzofuran intermediates **84** and **85** were prepared in all cases by deprotonation of phthalides **81** or **83**, respectively, with potassium bis(trimethylsilyl)amide (1.1 equiv) in THF (−78 °C, 30 min) and silylation with a mixture of chlorotrimethylsilane and triethylamine (1:1, ~3.0 equiv TMSCl; −20 °C for 0.5–3 min, then −78 °C). Immediate reaction of the unstable isobenzofuran with the dienophile at 50–60 °C then produced the Diels–Alder adducts. Condensation of isobenzofuran **84** (1.1 equiv) with *p*-benzoquinone provided the *endo* adduct **86** in ~75% yield (determined by <sup>1</sup>H NMR analysis of the crude reaction mixture using an internal standard; eq 3). Reaction of isobenzofuran **85** with quinone ketal **87** (1.2 equiv)<sup>79</sup> gave the *endo* Diels–Alder adducts **88** and **89** as a 1:1 mixture of diastereomers in 39% yield (56% based on recovered quinone ketal **87**; eq 4). Condensation of enedione

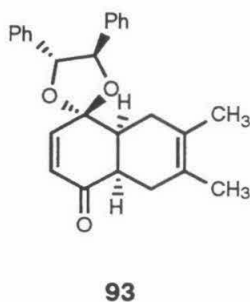


**90**<sup>80</sup> with isobenzofuran **85** (1.5 equiv) provided the *endo* adduct **91** (60%; eq 5). Desilylation and acetal cleavage of **91** with HF•pyridine complex buffered with pyridine in THF produced the tetracyclic compound **92** in 60% yield, notably, without epimerization

or aromatization (eq 6). Determination of the Diels–Alder selectivity for these products was based on long-range  $^1\text{H}$  NMR difference nOe enhancements.

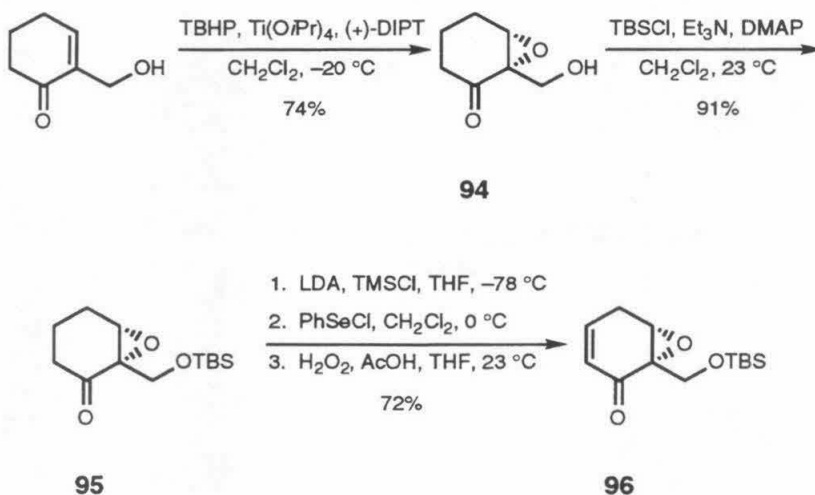


To probe the use of a simple enone as a dienophile the isobenzofuran **84** (1.1 equiv) was heated with 2-cyclohexen-1-one. No adduct was observed. Similarly, reaction of isobenzofuran **85** (2.5 equiv) with enone **93** (prepared by the thermal Diels–Alder reaction of quinone ketal **87** with 2,3-dimethyl-1,3-butadiene) under the above conditions did not produce any Diels–Alder adduct.



To probe systems more relevant to the synthetic plan, enone **96** was studied as a model for the B-ring of tetracycline. This compound was designed to contain  $\alpha$ -oxygenation as well as a protected  $\alpha$ -hydroxymethyl group that could serve as a handle for further functionalization or could, upon deprotection, activate the enone by hydrogen-bonding. Enone **96** was synthesized as outlined in Scheme IX. Sharpless asymmetric epoxidation of 2-(hydroxymethyl)-2-cyclohexen-1-one<sup>81</sup> was effected in 74% yield using

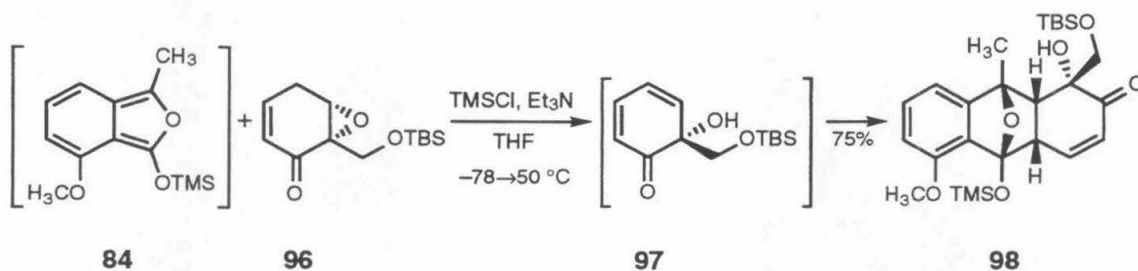
## Scheme IX



*tert*-butyl hydroperoxide (5.0 equiv), titanium(IV) isopropoxide (5.0 equiv), (L)-diisopropyl tartrate (6.0 equiv), and 4Å molecular sieves (30% w/w) in dichloromethane at  $-20\text{ }^\circ\text{C}$ .<sup>82</sup> The reaction proceeded in  $\geq 94\%$  enantiomeric excess as determined by  $^1\text{H}$  NMR analysis of the corresponding Mosher ester derivative.<sup>83,84</sup> Protection of alcohol **94** with *tert*-butyldimethylsilyl chloride (2.0 equiv), triethylamine (2.5 equiv), and DMAP (0.25 equiv) in dichloromethane provided ketone **95** in 91% yield. Introduction of  $\alpha,\beta$ -unsaturation into this substrate proved to be a non-trivial task. After much experimentation, the following sequence was found to be the most effective. Ketone **95** was deprotonated and trapped as its trimethylsilyl enol ether in situ (LDA (1.5 equiv), TMSCl (3.0 equiv), THF,  $-78\text{ }^\circ\text{C}$ ).<sup>85</sup> Addition of phenylselenenyl chloride (1.1 equiv,  $\text{CH}_2\text{Cl}_2$ ,  $0\text{ }^\circ\text{C}$ ) followed by oxidation of the resultant adduct with hydrogen peroxide (2.1 equiv, acetic acid (0.2 equiv), THF,  $0 \rightarrow 23\text{ }^\circ\text{C}$ ) provided the desired enone **96** in 72% overall yield.<sup>86</sup>

The isobenzofuran Diels–Alder reaction was then examined with enone **96**. Surprisingly, the reaction of the proposed isobenzofuran **84** (5.2 equiv) with enone **96** gave a single Diels–Alder adduct in 75% yield (higher yields were realized when the ratio

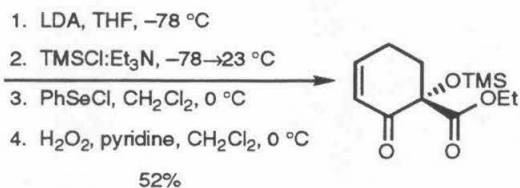
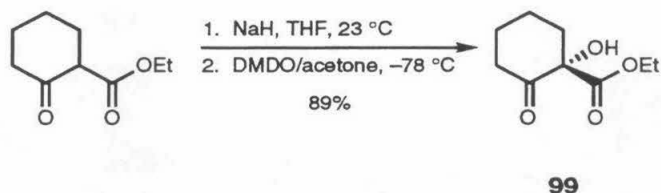
of chlorotrimethylsilane to triethylamine was <1:1). Careful analysis of the product indicated that opening of the epoxide had taken place prior to the Diels–Alder reaction to provide the adduct **98** with complete *endo* and facial selectivity (as determined by nOe studies). Presumably, epoxide opening occurs in situ upon heating in the presence of triethylamine. Since the isobenzofuran **84** is the more reactive diene, it reacts preferentially with the  $\gamma,\delta$ -double bond, a phenomenon observed in other cases when 2,4-cyclohexadienones react as dienophiles.<sup>77,87</sup> The cycloaddition takes place on the same face of the dienophile as the free hydroxyl group to generate the adduct **98** in high yield and with high selectivity.



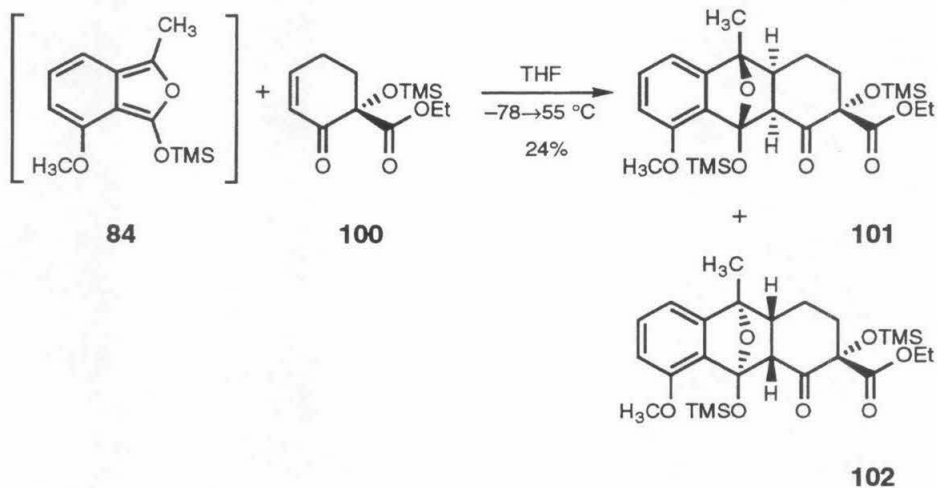
It was believed that an enone containing a 1,3-dicarbonyl unit, as in the actual right-hand half of tetracycline, would benefit from the potential for metal chelation as a means of activation of the dienophile. Thus, to more closely model the proposed right-hand portion of tetracycline, enone **100**, containing an  $\alpha$ -ester as well as a protected  $\alpha$ -hydroxyl group, was prepared. Toward this end, ethyl 2-cyclohexanonecarboxylate was deprotonated with sodium hydride (1.1 equiv) in THF and the resulting anionic species was hydroxylated with a solution of dimethyldioxirane (1.6 equiv) in an acetone and dichloromethane mixture (-78 °C) in 89% yield.<sup>88</sup> Alcohol **99** then underwent bis-silylation in the presence of lithium diisopropylamide (2.2 equiv, THF, -78 °C) and a solution of chlorotrimethylsilane and triethylamine (1:1, ~3.0 equiv TMSCl, -78→23 °C) to form a trimethylsilyl enol ether intermediate containing the silylated alcohol.  $\alpha$ -Alkylation of the TMS-enol ether with phenylselenenyl chloride (1.2 equiv, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C) was followed by oxidation and



elimination of the phenylselenoxide (hydrogen peroxide (3.1 equiv), pyridine (2.0 equiv),  $\text{CH}_2\text{Cl}_2:\text{H}_2\text{O}$ ,  $0\text{ }^\circ\text{C}$ ) to provide the racemic enone **100** in 52% overall yield.<sup>86</sup>

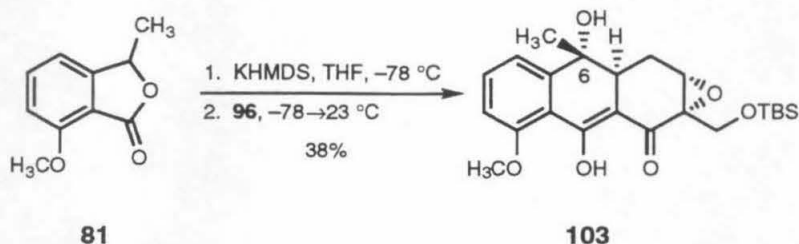


Treatment of enone **100** with the putative isobenzofuran **84** (1.3 equiv) at  $55\text{ }^\circ\text{C}$  provided a major Diels–Alder adduct **101** in 15% yield and a minor adduct **102** in 9% yield (26% and 17%, respectively, based on recovered **100**). The major and minor adducts appeared to be diastereomers based upon analysis of their nearly identical  $^{13}\text{C}$  NMR spectra. A comparison of the coupling constant for the Diels–Alder ring fusion (CH–CH) protons of **101** and **102** ( $J = 7.3\text{--}8.4\text{ Hz}$ ) versus previous *endo* ( $J = 9\text{--}10\text{ Hz}$ ) and *exo* ( $J = 7\text{--}8\text{ Hz}$ ) Diels–Alder adducts<sup>76</sup> indicated that these diastereomers likely



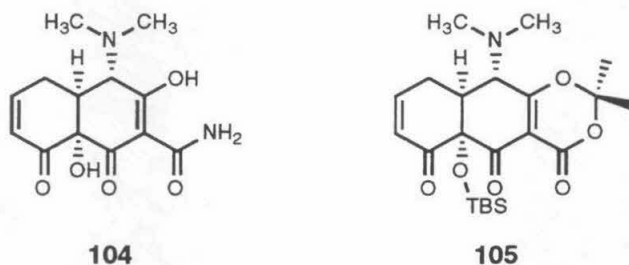
resulted from an *exo* Diels–Alder cycloaddition. This unexpected result, although not confirmed by nOe spectroscopic studies, further demonstrates the idiosyncrasies of the isobenzofuran Diels–Alder reaction. The adducts **101** and **102** are suspected to differ in their facial selectivity in the Diels–Alder reaction. However, given the dissimilarity of the adducts with the actual right-hand half of tetracycline, this lack of complete facial selectivity was not of great concern. The minor diastereomer **102**, tentatively assigned as the adduct resulting from attack of the isobenzofuran on the  $\beta$ -face of the enone, was contaminated by two very minor products that are likely the *endo* Diels–Alder adducts, indicating that the reaction is not completely selective for the *exo* Diels–Alder addition. Nevertheless, the formation of the *exo* Diels–Alder adducts **101** and **102** in a combined yield of 24% by a simple thermal reaction provided support for the proposed synthetic plan.

As an alternative to the isobenzofuran Diels–Alder reaction, a Michael addition and subsequent Dieckmann condensation sequence could be utilized to join the two proposed halves of tetracycline. This approach was briefly probed with enone **96**. Phthalide **81** (5.0 equiv) was deprotonated with KHMDS (5.2 equiv, THF,  $-78\text{ }^{\circ}\text{C}$ ) and the resulting enolate was condensed with enone **96** ( $-78\rightarrow 23\text{ }^{\circ}\text{C}$ ). The tricyclic product **103** was isolated in 38% yield. A minor amount of a compound tentatively identified as the simple Michael addition product was also isolated (19%). Analysis of **103** by nOe experiments indicated the presence of one inverted stereogenic center (C-6 position) relative to tetracycline. The decreased control over stereochemistry makes this route less attractive for the total synthesis of tetracycline.



## Studies Toward the Synthesis of the Right-Hand Half of Tetracycline

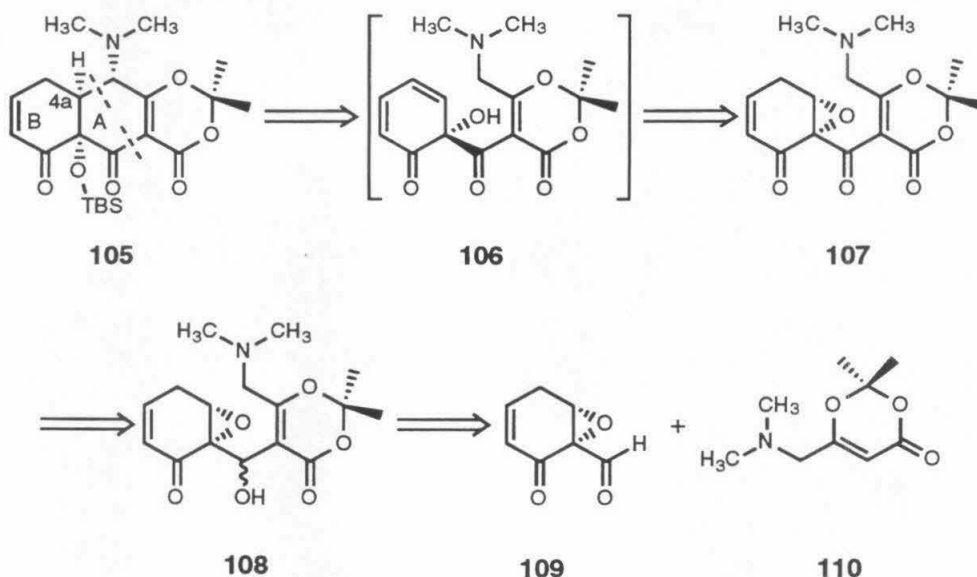
Encouraged by the favorable results of the isobenzofuran Diels–Alder reactions with various dienophiles, especially the  $\beta$ -keto ester **100**, the goal became the preparation of the fully functionalized right-hand half of tetracycline, ideally a protected form of the enone **104**. It was envisioned that the use of a bulky protecting group, such as a *tert*-butyldimethylsilyl ether, on the tertiary alcohol would influence the facial selectivity of the isobenzofuran Diels–Alder reaction. It was also desirable to find a practical protection scheme for the polar and acidic functionality of the  $\beta$ -keto amide. A dioxinone framework, containing a protected  $\beta$ -keto ester, appeared ideal for the job at hand. These substrates are readily converted into  $\beta$ -keto amides upon mild heating in the presence of an amine (such as ammonia).<sup>89</sup> Thus, enone **105** was selected as a suitably-protected precursor for the right-hand half of tetracycline.



Retrosynthetic analysis of enone **105** suggested the cleavage of the A ring as shown to preserve the dioxinone framework (Scheme X). Retrosynthetic cleavage of the top bond was performed first since it was thought that the C-4a stereocenter could be controlled better via an intramolecular reaction. An extended Michael-type reaction of the rigid dienolate generated within **106** onto the 2,4-cyclohexadienone subunit (a 6-exo-trig reaction) was anticipated to correctly set the C-4 and C-4a stereocenters (although correct introduction of the C-4 stereocenter would not be crucial, considering that it could be equilibrated to the desired epimer at the final stage of the synthesis). Based on previous findings from the isobenzofuran Diels–Alder reaction with enone **96**, this unstable

intermediate was envisioned to arise from the in situ base rearrangement of epoxide **107**. No literature precedent existed for a direct intramolecular nucleophilic addition of an enolate on to the epoxide of **107**.<sup>90</sup> The epoxide **107** could be prepared by the oxidation of alcohol **108**, which would arise from an aldol reaction between aldehyde **109** and the functionalized dioxinone core **110**. Efforts directed toward the preparation of **105** are now described.

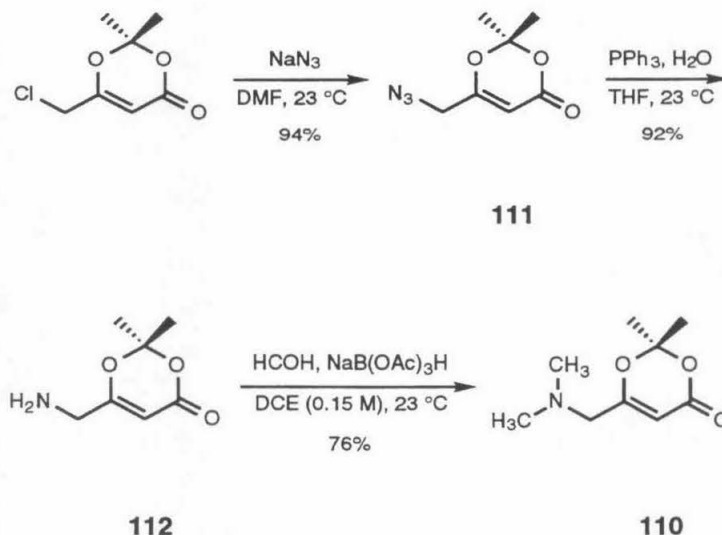
### Scheme X



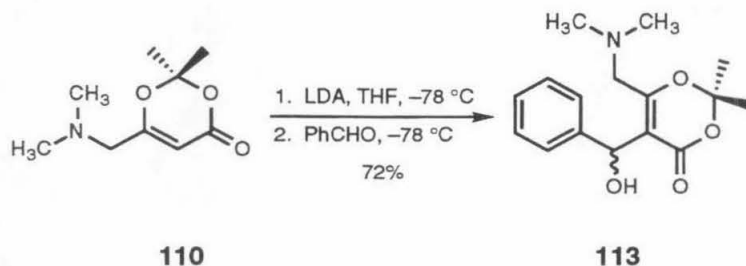
Dimethylamine **110** was readily prepared from the product of chlorination of commercially available 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (Scheme XI).<sup>91</sup> Efforts to displace 6-chloromethyl-2,2-dimethyl-1,3-dioxin-4-one directly using dimethylamine as a nucleophile were unsuccessful; however, reaction with sodium azide (1.1 equiv) in *N,N*-dimethylformamide resulted in clean conversion to the azide **111** (94%).<sup>92</sup> Reduction of the azide via the Staudinger reaction (triphenylphosphine (1.1 equiv), water (1.5 equiv), THF) provided the primary amine **112** in 92% yield.<sup>93</sup> Amine **112** then underwent reductive alkylation with formaldehyde (3.0 equiv) and sodium triacetoxyborohydride (4.0

equiv) in dichloroethane (0.15 M) to afford the desired dimethylamine **110** as a pale yellow solid (76%).<sup>94</sup>

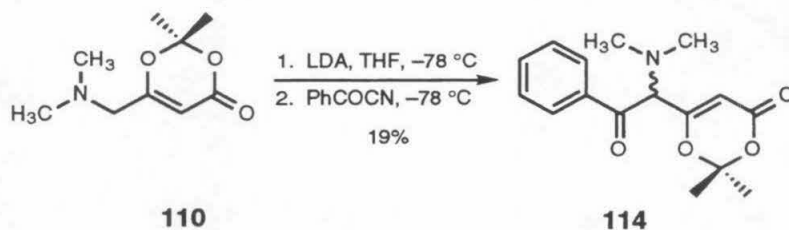
### Scheme XI



The dienolate of the parent structure, 2,2,6-trimethyl-4H-1,3-dioxin-4-one, tends to favor addition to aldehydes at its  $\gamma$ -carbon.<sup>89,95</sup> It was unclear what influence the dimethylamino group would have on the reactivity of the dienolate of **110**, and therefore a few control reactions were performed. Amine **110** (2.1 equiv) was deprotonated with lithium diisopropylamide (2.2 equiv) in THF (−78 °C, 35 min) and the resulting dienolate was condensed with benzaldehyde to give the  $\alpha$ -adduct **113** in 72% yield. The

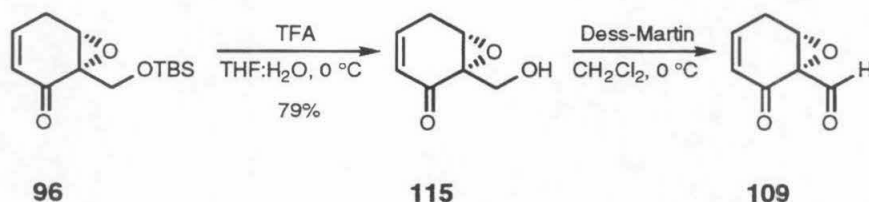


regiochemistry of the addition was determined by an NMR attached proton test (APT) experiment. Interestingly, when **110** (1.2 equiv) was deprotonated with LDA (1.3 equiv) in THF (−78 °C) and the resulting dienolate was treated with benzoyl cyanide, only the  $\gamma$ -addition product **114** was observed (19%). When KHMDS was utilized to deprotonate



amine **110** (THF,  $-78^\circ\text{C}$ ),  $\gamma$ -addition products were observed exclusively (*vide infra*). Thus, it appeared that dimethylamine **110** could be utilized for nucleophilic addition through either the  $\alpha$ - or  $\gamma$ -position of its dienolate by simply changing the electrophile or the counterion of the dienolate.

Having demonstrated the desired  $\alpha$ -reactivity of amine **110** in an aldol reaction, efforts were then directed toward preparation of the B-ring precursor. The synthesis of aldehyde **109** proceeded from the protected enone **96**, which was desilylated with trifluoroacetic acid (2.5 equiv) in a mixture of tetrahydrofuran and water (1:1) at  $0^\circ\text{C}$  to afford the volatile alcohol **115** (79%). Subsequent oxidation of the alcohol to the aldehyde proceeded only with Dess–Martin periodinane (1.2 equiv) in dichloromethane.<sup>96</sup> The isolation of **109** was complicated by its instability toward both aqueous work-up and silica gel; by-products were largely removed by multiple filtrations of the reaction mixture

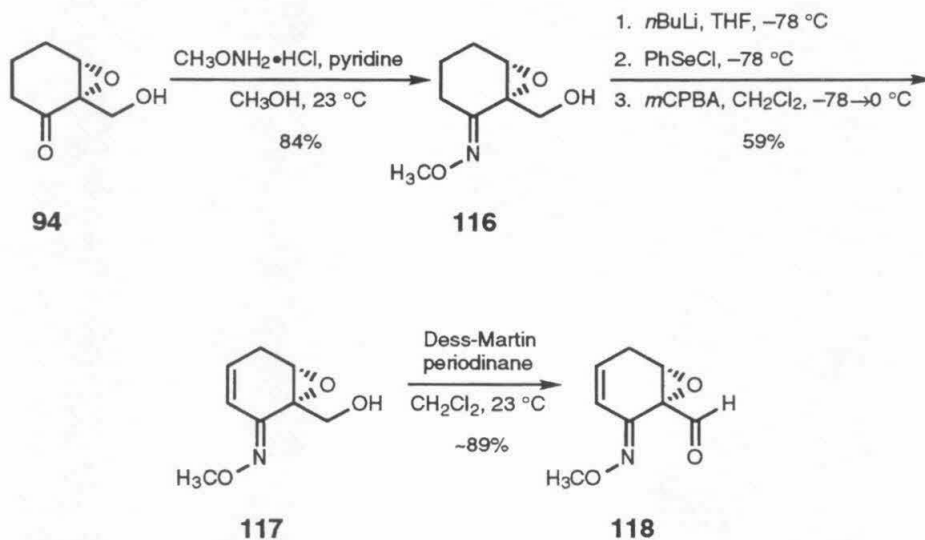


through Celite. The crude aldehyde **109** (excess) was then added to a solution of the lithium dienolate of amine **110** (generated with LDA in THF at  $-78^\circ\text{C}$ ). Unfortunately, this reaction merely led to the rapid decomposition of aldehyde **109**.

In an effort to increase the stability of aldehyde **109**, the carbonyl group was replaced with a methyloxime group. A more rapid and efficient synthesis of the target substrate was realized when the methyloxime functionality was introduced prior to double bond formation (Scheme XII). Thus, alcohol **94** was treated with methoxyamine

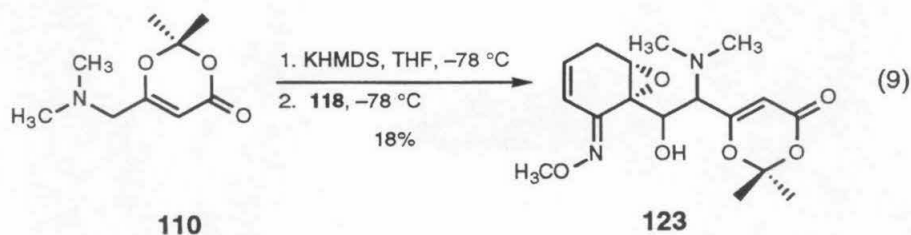
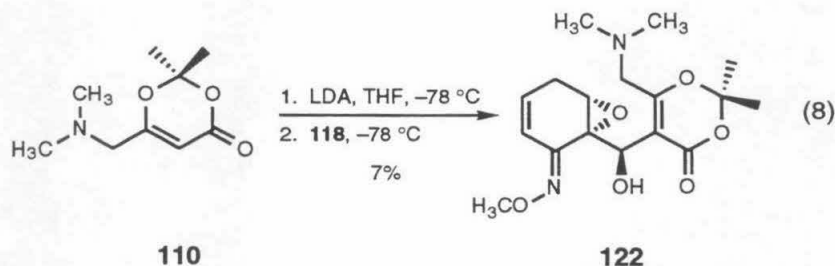
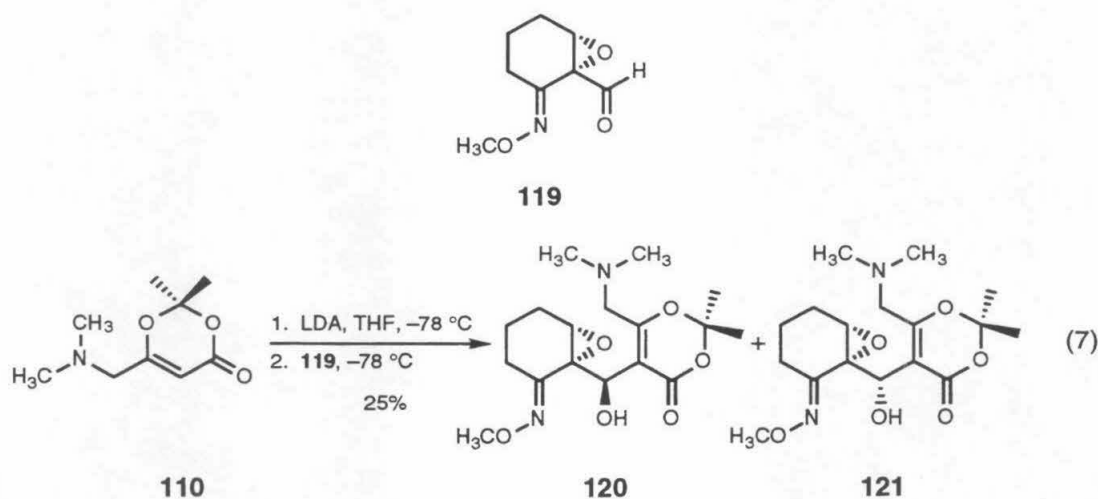
hydrochloride (2.0 equiv) and pyridine (3.0 equiv) in methanol to provide methyloxime **116** in 84% yield. Deprotonation of methyloxime **116** with *n*-butyllithium (2.2 equiv, THF,  $-78\text{ }^{\circ}\text{C}$ ) and subsequent reaction with phenylselenenyl chloride (1.2 equiv,  $-78\text{ }^{\circ}\text{C}$ ) afforded the  $\alpha$ -selenenylation product. This selenide was subjected in crude form to oxidation conditions (*m*-CPBA (1.5 equiv),  $\text{CH}_2\text{Cl}_2$ ,  $-78\rightarrow 0\text{ }^{\circ}\text{C}$ ) which, upon elimination of the intermediate selenoxide, produced the  $\alpha,\beta$ -unsaturated methyloxime **117** in 59% overall yield (12% recovered **116**). It was gratifying to observe that oxidation of **117** with Dess–Martin periodinane (1.5 equiv,  $\text{CH}_2\text{Cl}_2$ ) afforded a product that was stable to the standard reductive aqueous work-up. In addition, aldehyde **118** could be quickly purified by flash column chromatography, although it was typically used in crude form ( $\sim 89\%$ ).

### Scheme XII



Aldol reactions between the lithium dienolate of amine **110** and aldehydes **118** and **119** (prepared by the oxidation of **116** with Dess–Martin periodinane) were carried out as described above. An aldol reaction with aldehyde **119** gave the  $\alpha$ -adducts **120** and **121** as separable diastereomers (18% and 7%, respectively, 46% combined yield based on recovered **119**; eq 7). The stereochemical assignment of the diastereomers was chosen arbitrarily. Similarly, an aldol reaction with aldehyde **118** produced  $\alpha$ -adduct **122** (7%,

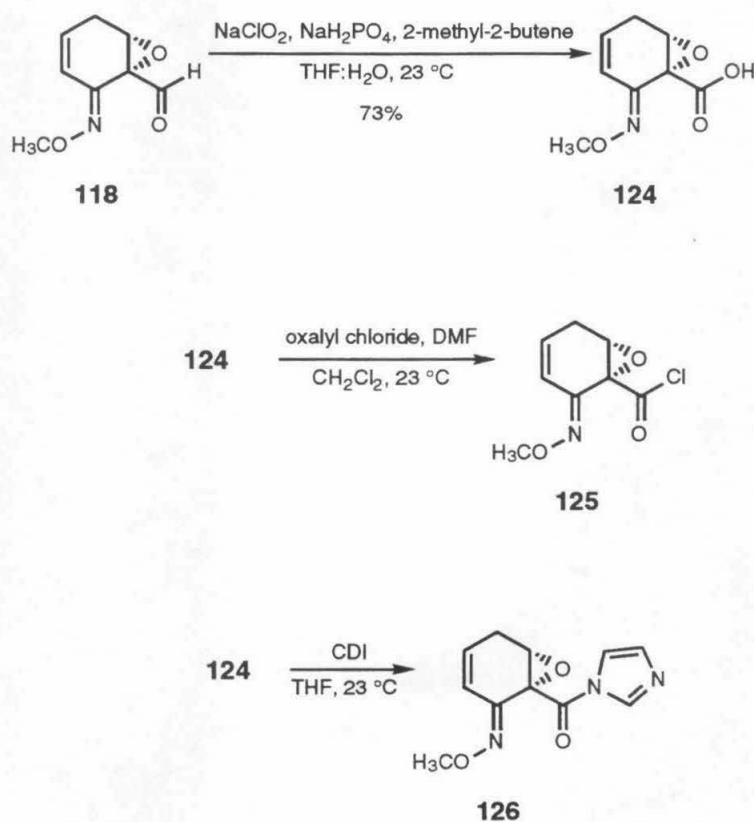
significant amounts of starting material remained), based on its similarity to adduct **120** (eq 8). The diastereomer of **122** was visible by TLC; however, this more polar product could not be isolated chromatographically. The yields of these reactions were not significantly improved by the use of a titanium dienolate (generated from the lithium dienolate of amine **110** and chlorotitanium triisopropoxide) or with additives (such as  $\text{CeCl}_3$ ), although the reaction was selective for one diastereomer when using the titanium dienolate. When the potassium dienolate of amine **110** (1.5 equiv; generated with KHMDS (1.7 equiv) in THF,  $-78^\circ\text{C}$ ) was condensed with aldehyde **118**, only the  $\gamma$ -addition product **123** was observed ( $>18\%$  yield; eq 9).





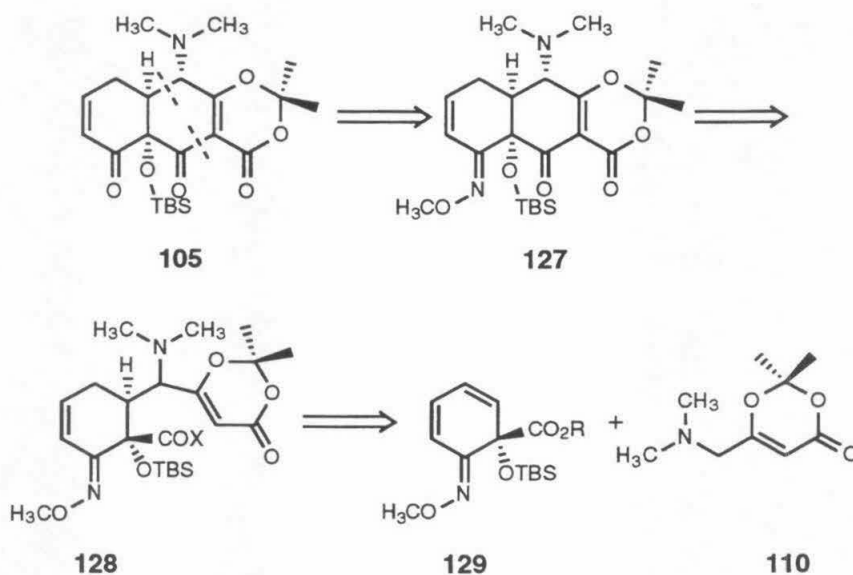
The inability to produce significant amounts of the desired aldol adduct led to the exploration of the use of an activated ester as the electrophile. Oxidation of aldehyde **118** with sodium chlorite (10.0 equiv) in the presence of sodium dihydrogenphosphate (13.4 equiv) and 2-methyl-2-butene (28.3 equiv) in a mixture of tetrahydrofuran and water provided carboxylic acid **124** in 73% yield (Scheme XIII).<sup>97</sup> Acid chloride **125** was then prepared from **124** in situ (oxalyl chloride (5.0 equiv), DMF (cat.),  $\text{CH}_2\text{Cl}_2$ ). Similarly, activated ester **126** was prepared in situ by treatment of carboxylic acid **124** with 1,1'-carbonyldiimidazole (1.1 equiv) in THF (23 °C, 1.5 h). Attempts to couple the dienolate of amine **110** (formed with either LDA, KHMDS, or LHMDS) with acid chloride **125** and imidazolide **126** were surprisingly unsuccessful. Either no reaction was observed or amide formation with the amide base occurred.

Scheme XIII



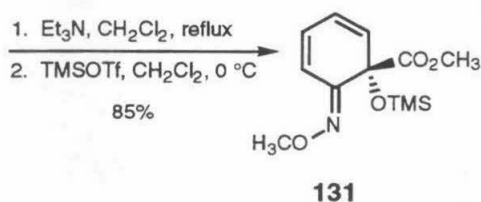
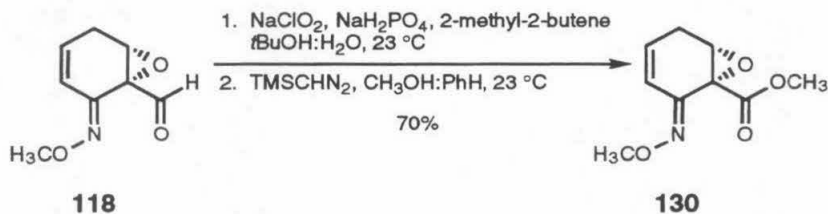
It still remains unclear as to why the methyloxime series of substrates did not perform better in the above reactions. This may be a reflection of the steric hindrance imparted by the quaternary  $\alpha$ -center of the aldehydes **118** and **119** and activated esters **125** and **126**. The proposed order of steps in the synthesis of the right-hand half was therefore reversed (Scheme XIV). Thus, the later formation of the lower ring bond was expected to proceed more favorably by an intramolecular reaction with an aldehyde (**128**, X = H) or an activated ester (**128**, X = Cl, imidazole). The formation of substrate **128** by the intermolecular addition of the potassium dienolate of amine **110** to pre-formed 2,4-cyclohexadienone substrate **129** via an extended Michael reaction was then targeted.

Scheme XIV

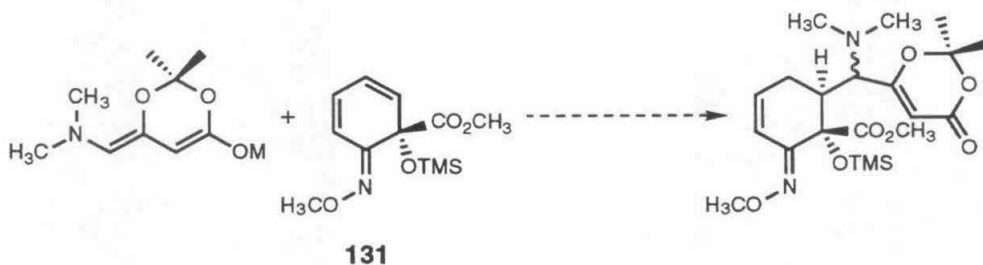


The diene methyloxime **131** was prepared as follows. Aldehyde **118** was oxidized to the corresponding carboxylic acid as described above, and, after extractive isolation, the crude acid was treated with (trimethylsilyl)diazomethane (1.8 equiv) in a solution of methanol in benzene to provide methyl ester **130** in 70% yield from **118**.<sup>98</sup> Reaction of ester **130** with excess triethylamine (10.0 equiv) in refluxing dichloromethane gave the

intermediate dienyl alcohol which was protected in situ as its trimethylsilyl ether **131** by addition of trimethylsilyl trifluoromethanesulfonate (2.0 equiv) at 0 °C (85% overall yield).



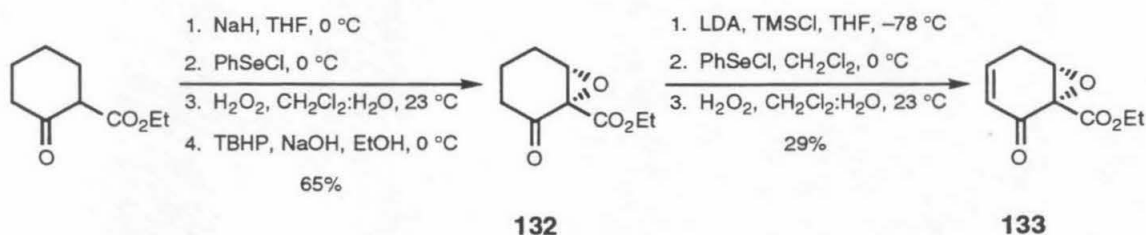
With the conjugated methyloxime **131** in hand, efforts to couple it with amine **110** via an extended Michael reaction were initiated. The potassium dienolate of dimethylamine **110** was initially prepared to favor  $\gamma$ -addition (1.0 equiv  $\text{KHMDs}$ , THF,  $-78$  °C) and was added in excess to a solution of methyloxime **131** in tetrahydrofuran. Minor amounts of desilylated starting material, but no adduct formation, were observed. Addition of **131** to the lithium dienolate of dimethylamine **110** was also unsuccessful. The trimethylsilyl enol ether of dimethylamine **110** was prepared ( $\text{KHMDs}$  (1.1 equiv), THF,  $-78$  °C; chlorotrimethylsilane (2.0 equiv),  $-78 \rightarrow 23$  °C; characterized by  $^1\text{H}$  NMR) and combined in excess with methyloxime **131**. Analysis of the crude reaction mixtures indicated that decomposition of the trimethylsilyl enol ether had occurred. The addition of Lewis acids to



these reactions gave no improvement. In all cases, the conjugated methyloxime **131** remained unchanged.

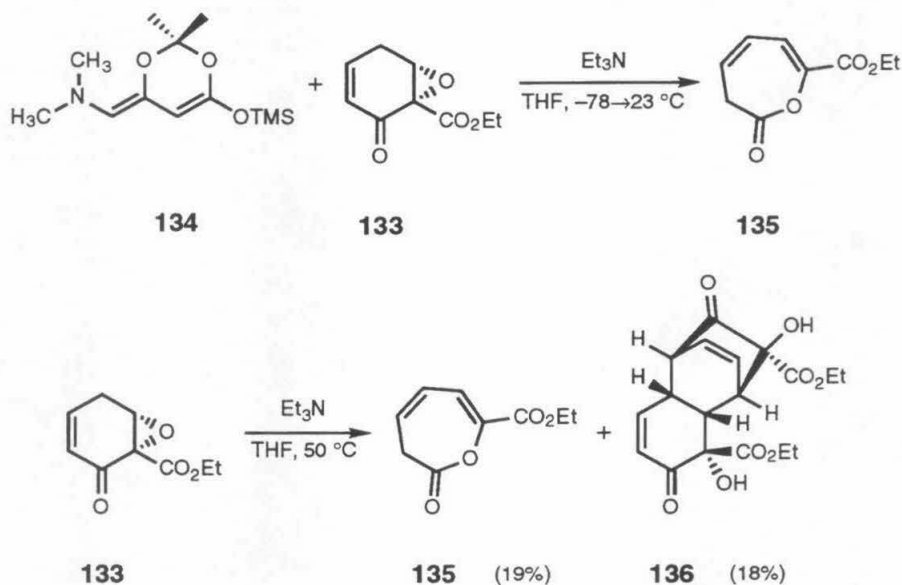
Although substitution of the carbonyl group with a methyloxime group provided enhanced stability, these compounds were ultimately too unreactive for the purposes described here. Conversion of these advanced intermediates to the corresponding ketones was then pursued, but cleavage of the methyloxime functionality at various stages (substrates **130** and **131**) was unsuccessful.<sup>99–101</sup>

Because the oxidation of alcohol **115** to the aldehyde was problematic, an alternative route to the more advanced ester precursor was sought. 2-Carbethoxy-2-cyclohexen-1-one was readily prepared from 2-carbethoxycyclohexanone by the method of Reich and co-workers.<sup>86</sup> Treatment of the unstable crude enone with *tert*-butyl hydroperoxide (3.0 equiv) and sodium hydroxide (0.1 equiv) in ice-cooled ethanol provided the stable, racemic epoxide **132** in 65% yield.<sup>102</sup> In situ deprotonation and silylation of ketone **132** (LDA (1.2 equiv), TMSCl (2.5 equiv), THF,  $-78\text{ }^{\circ}\text{C}$ ) followed by the addition of phenylselenenyl chloride (1.2 equiv) in dichloromethane ( $0\text{ }^{\circ}\text{C}$ ) gave an  $\alpha$ -phenylselenide. Direct oxidation of the crude selenide and subsequent selenoxide elimination then ensued upon treatment with hydrogen peroxide (2.2 equiv) in a mixture of dichloromethane and water ( $0\rightarrow 23\text{ }^{\circ}\text{C}$ ) to provide the enone **133** in 29% yield from ketone **132**.



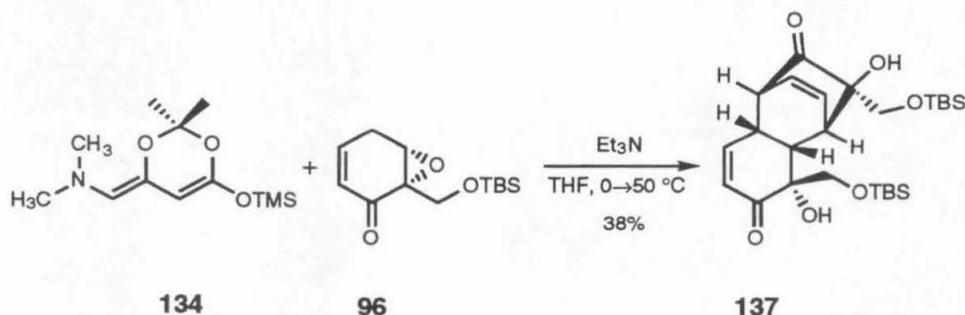
Transformation of the enone **133** into the corresponding 2,4-cyclohexadienone and its subsequent reaction in situ with the dienolate of amine **110** via an extended Michael addition was then pursued. Enone **133** was combined with trimethylsilyl enol ether **134**

(6.9 equiv) in THF ( $-78 \rightarrow 23$  °C) in the presence of triethylamine (6.9 equiv). Lactone **135**, characterized by  $^1\text{H}$  NMR,  $^1\text{H}$ - $^1\text{H}$  decoupling,  $^{13}\text{C}$  NMR, and FTIR analysis, was the only product observed (12% isolated yield). The treatment of enone **133** alone with triethylamine (5.0–10.0 equiv) in THF (0.035–0.047 M) resulted in the formation of the lactone **135** (19–34%) as well as the dimer **136** (13–19%). The latter product is believed to arise by an inverse electron demand Diels–Alder reaction of the intermediate 2,4-cyclohexadienone, which acts as both the diene and the dienophile. According to literature precedent, the reaction is believed to have proceeded with *endo* selectivity and the designated regiochemistry.<sup>87</sup> The (racemic) product **136** appeared by  $^1\text{H}$  NMR to be a single diastereomer, tentatively assigned as the one in which the hydroxyl groups are in close proximity in the transition state of the cycloaddition reaction.<sup>87d</sup>

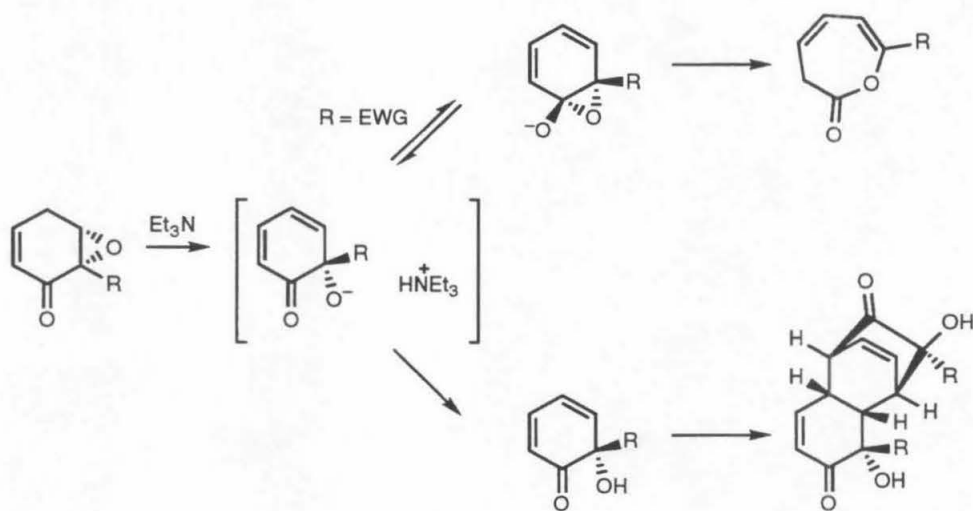


To avoid the dual reactivity displayed by an enone containing an  $\alpha$ -ester moiety, dienone formation from enone **96** was investigated. Reaction of the optically pure enone **96** with trimethylsilyl enol ether **134** (3.4–4.8 equiv) in the presence of triethylamine (10.0 equiv) or a mixture of chlorotrimethylsilane and triethylamine (1:1,  $\sim 10.0$  equiv  $\text{Et}_3\text{N}$ ) in THF (0.032–0.039 M) from  $-78 \rightarrow 50$  °C did not lead to the desired adduct

formation. Instead, the Diels–Alder dimer **137** was isolated as a single diastereomer in 35–40% yield. Again, the facial selectivity of the Diels–Alder reaction was presumed to occur through a transition state placing the hydroxyl groups in close proximity.



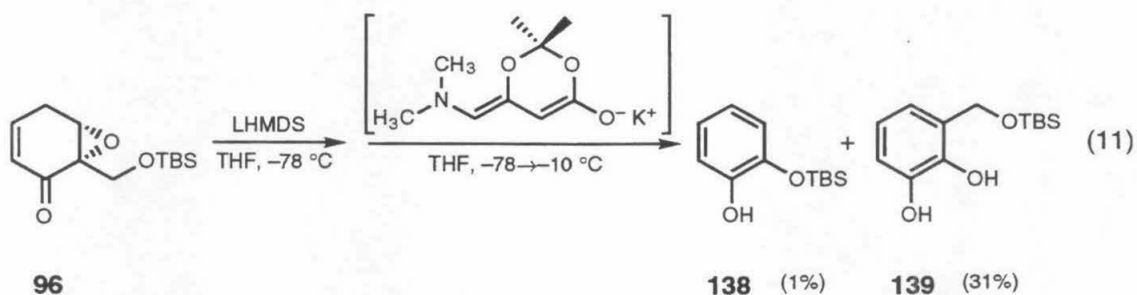
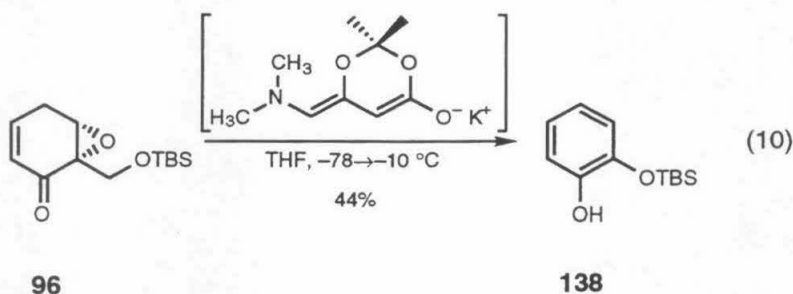
The above results suggested that the desired 2,4-cyclohexadienone intermediate was not isolable in monomeric form. In the case of enone **133**, the intermediate dienone underwent ring expansion, presumably favored by the presence of the electron-withdrawing ester moiety (Figure 8). In contrast, enone **96**, without the electron-withdrawing group, cannot undergo this ring-expansion reaction. Thus, enones such as



**Figure 8.** Proposed mechanism for dienone formation and rearrangement.

**133** were shown to be ineffective substrates for a route utilizing an intermediate 2,4-cyclohexadienone. These results also suggested that the trimethylsilyl enol ether **134** was not reactive enough for use in an extended Michael addition reaction with the dienone.

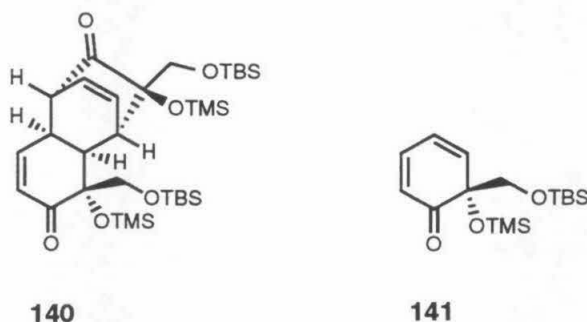
The next step was to discern whether these 2,4-cyclohexadienone intermediates could be formed under the influence of a strong base at lower temperatures such that the more reactive dienolate of amine **110** could be used as the nucleophilic species. To test this, a tetrahydrofuran solution of enone **96** was added to an excess of the potassium dienolate of dimethylamine **110** (2.3 equiv) in THF and the resultant reaction mixture was then warmed from  $-78 \rightarrow 10$  °C. The enone was converted to phenol **138** (44%) at low temperature (eq 10). Treatment of enone **96** with LHMDS (1.1 equiv) in tetrahydrofuran ( $-78$  °C) and subsequent reaction of this solution with the potassium dienolate of amine **110** (1.2 equiv) in THF ( $-78 \rightarrow 10$  °C) provided phenol **138** (1%) and catechol **139** (20–30%; eq 11). These results indicated that enone **96** was undergoing deprotonation and



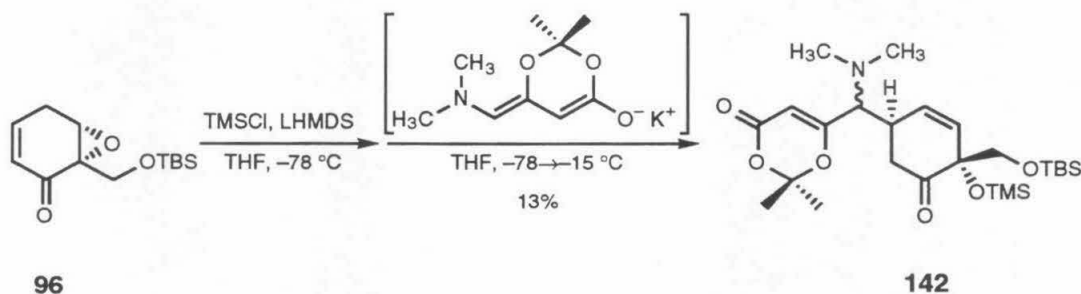
subsequent ring opening of the epoxide, but that the dienone alkoxide intermediate was apparently rearranging rapidly to the aromatic products. In an attempt to access the intermediate dienone alcohol rather than the dienone alkoxide, a catalytic base deprotonation

system (amine **110** (1.1 equiv), KO<sup>t</sup>-Bu (1.3 equiv), DMSO, THF, -20→-10 °C) was examined, but phenol **138** was still the major product (29%).

From these results, it seemed likely that trapping the dienone alkoxide intermediate as an ether might prevent the substrate from undergoing rearrangement to the aromatic products, and the formation of a 2,4-cyclohexadienone silyl ether in situ was next examined. It was found that when enone **96** was deprotonated with KHMDS or LHMDS in the presence of chlorotrimethylsilane and then condensed with the potassium dienolate of amine **110**, the dimer product **140** was observed as a single (enantiomerically pure) diastereomer. This time, it was expected that the bulky trimethylsilyl ether groups were on the outer face of the transition state, leading to the diastereomer shown. This result provided evidence that the silylated 2,4-cyclohexadienone **141** was in fact being generated.



Formation of the silylated dienone **141** (**140** (1.0 equiv), LHMDS (1.2 equiv), TMSCl (1.3 equiv), THF, -78 °C) under more dilute conditions (0.04 M vs 0.15 M) and subsequent transfer of the potassium dienolate of dimethylamine **110** (2.8 equiv) via cannula into the unstable dienone solution (-78→-15 °C) did, in fact, provide an adduct (**142**, 13% yield) in addition to the phenol **138** (30%) and the diol **139** (8%). However,

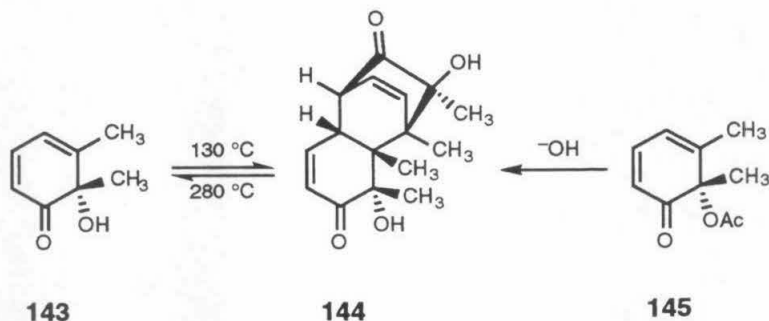




product **142**, isolated as a 1:2.5 mixture of diastereomers, presumably both from attack at the  $\beta$ -face of the dienone, was determined to be the 1,4-Michael addition product by  $^{13}\text{C}$  NMR analysis.

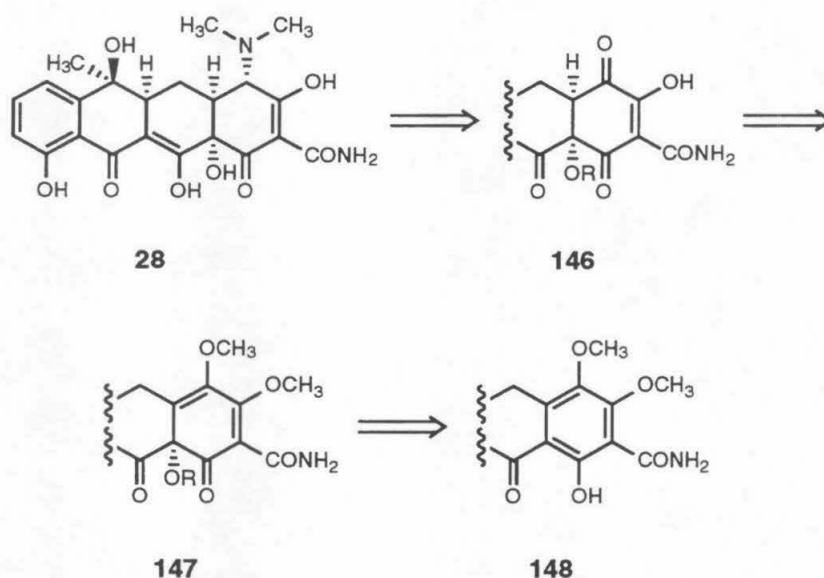
### A Route to the Right-Hand Half by Phenolic Oxidation

Further examination of the literature of 2,4-cyclohexadienone substrates provided useful information concerning dienone synthesis and stability. 6-Hydroxy-6-alkyl-2,4-cyclohexadienones such as **143** can be obtained in situ through the retro Diels–Alder reaction of the dimer **144**.<sup>87c,103</sup> The monomers dimerize at ambient temperature or above, depending upon the stereoelectronics of the substrate. The initial preparation of the cyclohexadienone, and subsequently its dimer, proceeds via the *ortho* oxidation of a phenol precursor with, for example, an oxidant such as sodium periodate.<sup>87,104</sup> Alternatively, dimer **144** can be accessed through the hydrolysis of a 6-acetoxy-6-alkyl-2,4-cyclohexadienone such as **145**.<sup>87c,105</sup> The presence of a 6-acetoxy group apparently makes the monomer dienone substrate more stable, even allowing for its purification by column chromatography. Compounds such as **145** are typically synthesized by the Wessely oxidation in one step from the substituted phenols.<sup>106</sup> This transformation, which utilizes lead(IV) acetate as the oxidant typically in acetic acid as the solvent, provides products with *o*-oxidation preferentially at the substituted carbon and operates optimally with electron-rich aromatic rings.



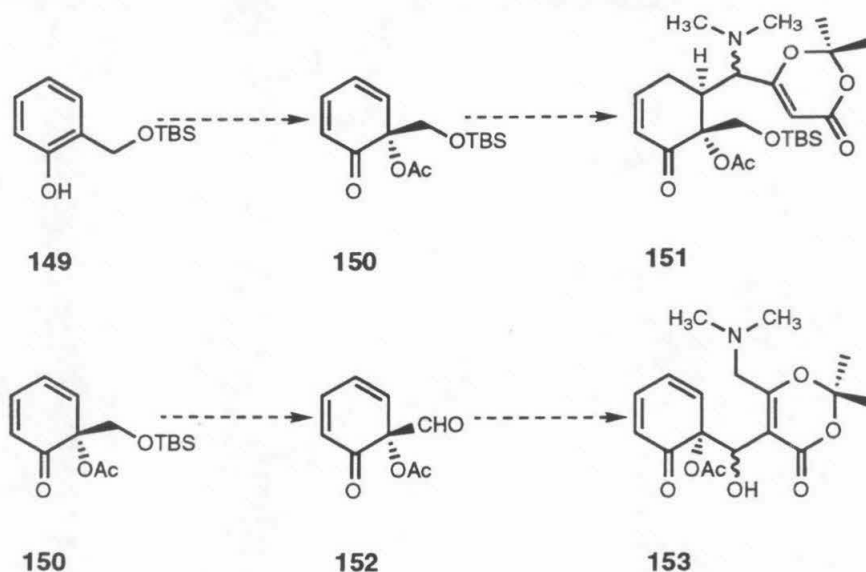
The direct oxidation of a phenolic system to access a 2,4-cyclohexadienone intermediate would provide a much more concise route to the synthesis of the right half of tetracycline since the starting materials would be commercially available or trivial to prepare. Interestingly, Barton and co-workers researched this strategy for the synthesis of the A ring of tetracycline **28** (Scheme XV).<sup>107</sup> Under their plan, the crucial oxygenation at C-12a would arise from the dearomatization of the A ring via phenol oxidation of intermediate **148**. Although several conditions were investigated for this transformation, Barton and co-workers were only able to *o*-hydroxylate simple one-ring aromatic phenols.

Scheme XV

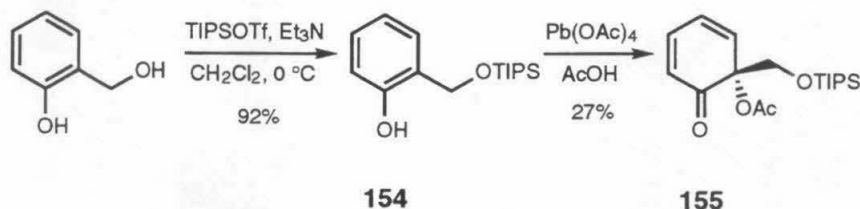


For this work, the suggested stability of the 6-acetoxy-2,4-cyclohexadienones warranted an evaluation of their use in the synthetic plan for the right half of tetracycline. The most obvious way to incorporate this change would be to prepare the cyclohexadienone **150** from Wessely oxidation of the phenol precursor **149** as a stable (racemic) starting material for more controlled examination of an extended Michael addition reaction with the dienolate of amine **110**. Alternatively, the stable cyclohexadienone **150**

could serve as a new starting material for subsequent aldehyde formation to give the proposed substrate **152**. An aldol reaction between **152** and the lithium dienolate of dimethylamine **110** could potentially provide adduct **153**, which could then undergo a regiochemically and stereochemically more favorable intramolecular addition to the conjugated dienone.

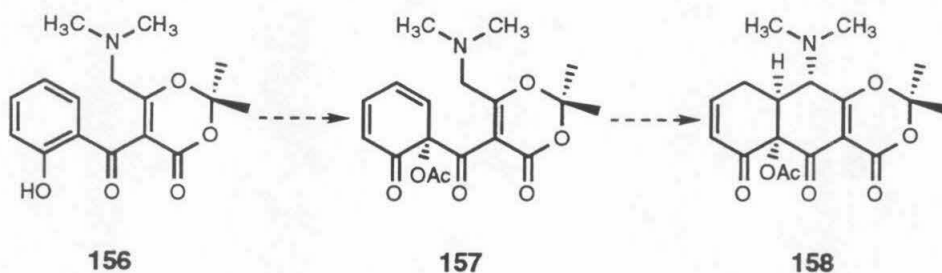


To test the feasibility of the Wessely oxidation for the one step preparation of 2,4-cyclohexadienones from simple phenol precursors, 2-hydroxybenzyl alcohol was protected as its silyl ether with the more acid stable triisopropylsilyl group. Thus, triisopropylsilyl ether **154** was prepared by treatment of the alcohol with TIPSOTf (1.1 equiv) and triethylamine (1.5 equiv) in dichloromethane (0 °C) in 92% yield. Oxidation of phenol **154** with lead(IV) acetate (1.5 equiv) in acetic acid did provide the 2,4-cyclohexadienone **155** as a stable yellow oil in 27% yield.<sup>106,108</sup> None of the desired product was observed upon



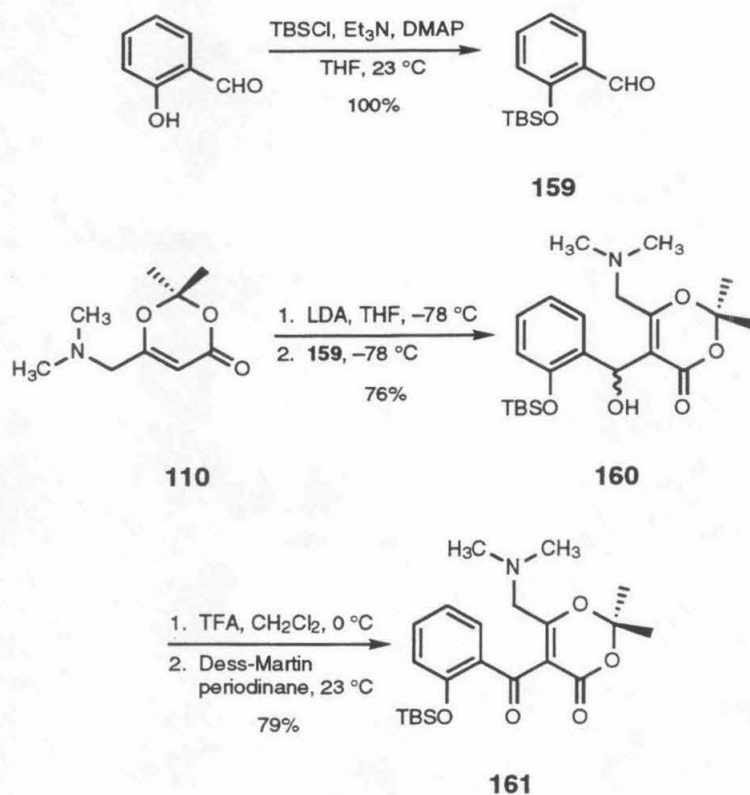
phenol oxidation of **154** with iodobenzene diacetate, iodobenzene bis(trifluoroacetate), or manganese(III) acetate.<sup>109,110</sup> The further functionalization of cyclohexadienone **155** was not pursued.

Perhaps a more exciting way to incorporate this methodology for the formation of a stable 2,4-cyclohexadienone would be to oxidize a highly functionalized phenol precursor, such as substrate **156**. The resultant 2,4-cyclohexadienone **157** would then need only undergo intramolecular addition, perhaps even under the reaction conditions for the oxidation, to effect the formation of the AB ring system (**158**). Such a route would constitute a remarkably rapid synthesis of the bicyclic right half of tetracycline.

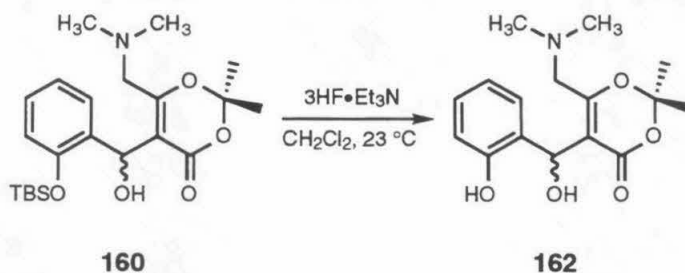


This synthetic strategy was pursued in the following manner. Salicylaldehyde was protected as its *tert*-butyldimethylsilyl ether **159** with TBSCl (2.0 equiv), triethylamine (3.0 equiv), and DMAP (cat.) in tetrahydrofuran in quantitative yield (Scheme XVI). An aldol reaction between the lithium dienolate of amine **110** (generated with LDA (1.2 equiv) in THF at  $-78\text{ }^{\circ}\text{C}$ ) and aldehyde **159** (1.3 equiv, THF,  $-78\text{ }^{\circ}\text{C}$ ) provided alcohol **160** in 76% yield. Oxidation of the resultant secondary alcohol to a ketone proved to be a non-trivial procedure. The use of Dess–Martin periodinane, pyridinium dichromate, pyridinium chlorochromate, or Swern conditions was unsuccessful.<sup>96,111</sup> However, prior treatment of alcohol **160** with trifluoroacetic acid (1.1 equiv,  $\text{CH}_2\text{Cl}_2$ ,  $0\text{ }^{\circ}\text{C}$ ) to protonate the dimethylamino group and subsequent oxidation with Dess–Martin periodinane (1.5 equiv,  $23\text{ }^{\circ}\text{C}$ ) resulted in the formation of ketone **161** in 79% yield.

## Scheme XVI

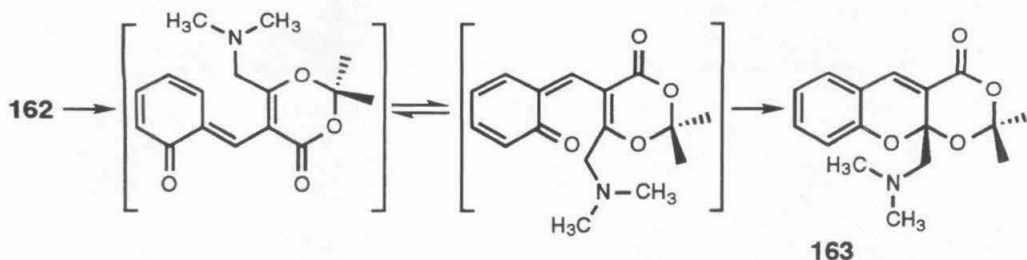


In order to test the Wessely oxidation, the deprotection of alcohol **160** was first necessary. Desilylation of **160** with triethylamine trihydrofluoride in dichloromethane gave the desired diol **162** by analysis of the crude  $^1\text{H}$  NMR. Although the product was visible by TLC, the isolation and further characterization of **162** proved difficult due to its



conversion to the less polar compound **163** with time or under acidic conditions. This by-product is proposed to form via the dehydration of diol **162** and the subsequent electrocyclic rearrangement of the intermediate quinone methide (Figure 9). Nevertheless, oxidation reactions were carried out on the crude diol **162** before its conversion to the

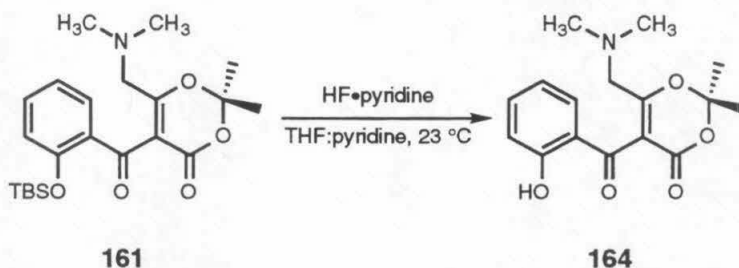
rearranged amine **163**. Reaction of diol **162** with lead(IV) acetate in acetic acid or dichloromethane,<sup>112</sup> however, resulted only in the rapid decomposition of the crude starting material.



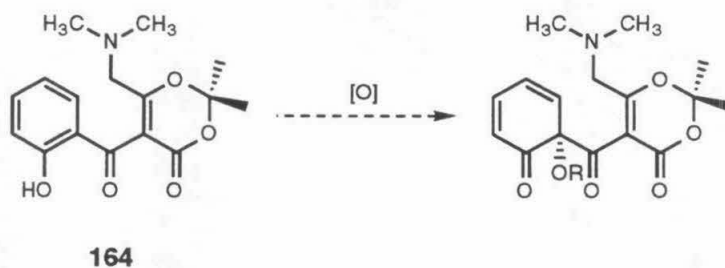
**Figure 9.** Proposed mechanism for a quinone methide rearrangement to generate **163**.

Due to the lability of the benzyl alcohol of **162**, a protected version of this compound was targeted. Protection of the secondary alcohol as a *tert*-butyldimethylsilyl or triisopropylsilyl ether proceeded readily; however, selective deprotection of the TBS aryl ether was difficult. The mono-protected phenols were unstable, and efforts to oxidize the phenols with lead(IV) acetate to the desired 2,4-cyclohexadienone substrates were unsuccessful.<sup>113</sup>

An alternate way to avoid the formation of dimethylamine **163** from substrates with a labile benzylic position would be to make use of the advanced ketone substrate. Therefore, the deprotection and subsequent phenol oxidation of ketone **161** was pursued. The desilylation of ketone **161** was realized using the HF•pyridine complex buffered with pyridine in tetrahydrofuran. The keto alcohol **164** was isolated in low crude yield (<50%).



With phenol **164** in hand, efforts turned toward its oxidation to the desired 2,4-cyclohexadienone product. Oxidation of phenol **164** with lead(IV) acetate in acetic acid proved disappointing. In dioxane, a new product was observed containing altered methylene protons but no acetate group. Decomposition of the starting material was observed in other solvents, even with prior protonation of the dimethylamino group with trifluoroacetic acid. A wide range of oxidants were also examined, to include benzoyl peroxide, sodium periodate, sodium tetraperoxymolybdate, iodobenzene diacetate, iodobenzene bis(trifluoroacetate), dimethyldioxirane, and *m*-chloroperoxybenzoic acid, but decomposition of the starting material was observed in almost every case.<sup>87,104</sup>

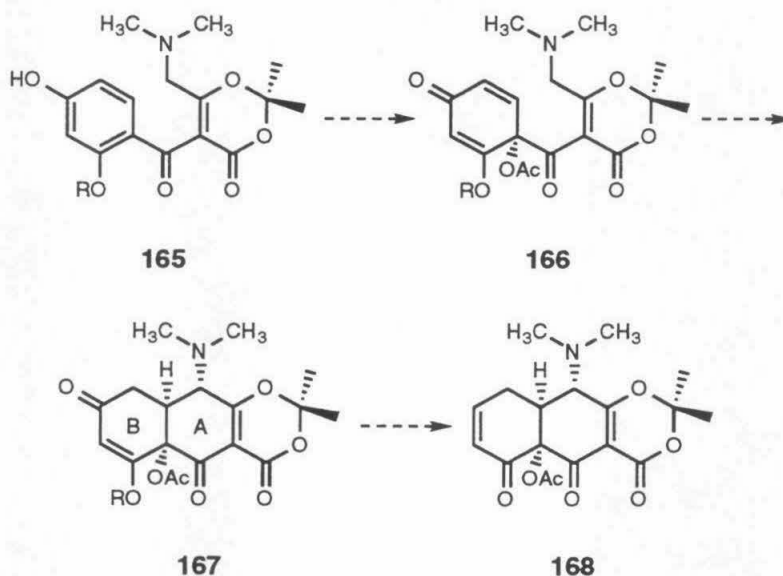


Some insight into the reactions performed under acidic conditions was provided by following the reaction of phenol **164** and iodobenzene bis(trifluoroacetate) in acetic acid-*d*<sub>6</sub> by <sup>1</sup>H NMR. It was found that phenol **164** did not react with the reagent under these conditions. Rather, slow hydrolysis of the ketal group and subsequent decomposition of the starting material was observed. Notably, the methylene protons of phenol **164** did not undergo deuterium exchange in the acidic medium as they typically did in related systems (vide infra).

The difficulties experienced in the oxidation attempts with diol **162** and phenol **164** demonstrate the weaknesses of the Wessely oxidation. Its sensitivity to the electronic nature of the aromatic ring typically results in low yields and mixtures of products.<sup>106</sup> To circumvent this problem, a more electron-rich system was considered. The strategic placement of an additional hydroxyl group on the aromatic ring now allowed the option of synthesizing a 2,5-cyclohexadienone substrate (**166**, Scheme XVII). The *p*-oxidation of

phenols, typically performed with iodobenzene diacetate or iodobenzene bis(trifluoroacetate), is a more common and reliable transformation than the *o*-oxidation of phenols.<sup>114</sup> Such a 2,5-cyclohexadienone **166** could then undergo an intramolecular Michael addition to form the bicyclic substrate **167**. Selective reduction of the B-ring ketone of **167** followed by deprotection of the ether and elimination of the alcohol under acidic conditions would effect the transposition of the enone to give the target substrate **168**.

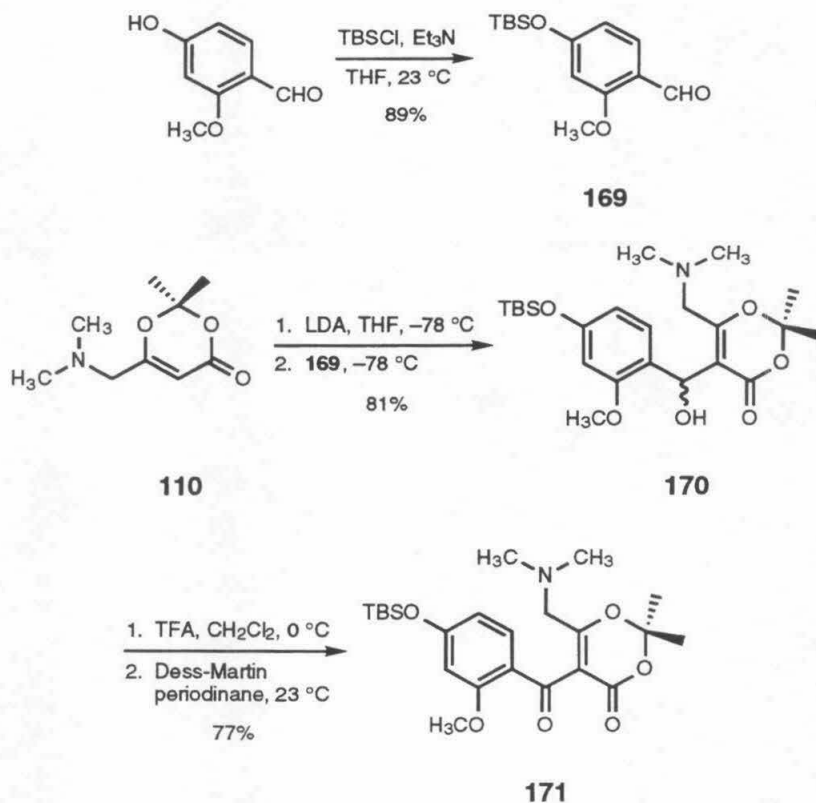
### Scheme XVII



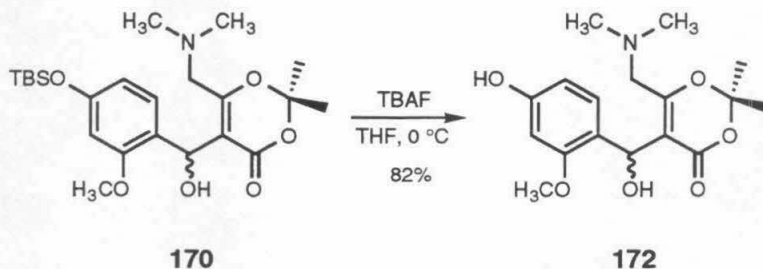
This route was pursued in the following manner (Scheme XVIII). Commercially available 4-hydroxy-2-methoxybenzaldehyde was protected as its *tert*-butyldimethylsilyl ether **169** with TBSCl (1.4 equiv) and triethylamine (1.5 equiv) in tetrahydrofuran (89%). Condensation of the lithium dienolate of amine **110** (generated with LDA (1.1 equiv) in THF,  $-78\text{ }^{\circ}\text{C}$ ) with aryl aldehyde **169** (1.2 equiv, THF,  $-78\text{ }^{\circ}\text{C}$ ) provided the aldol adduct **170** in 81% yield. Oxidation of alcohol **170** to ketone **171** was accomplished in 77% yield by protonation of the dimethylamino group of **171** with TFA (1.1 equiv) in dichloromethane ( $0\text{ }^{\circ}\text{C}$ ) and subsequent oxidation with Dess–Martin periodinane (1.5 equiv,  $23\text{ }^{\circ}\text{C}$ ).



## Scheme XVIII

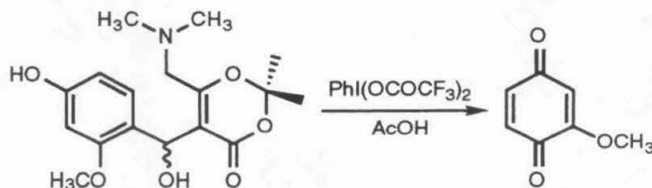


Deprotection of the adduct **170** required considerably stronger reaction conditions than in previous systems. Desilylation of **170** was executed with tetrabutylammonium fluoride (1.1 equiv) in tetrahydrofuran (0 °C) to give diol **172** in 82% yield. This compound was stable to column chromatography. In fact, most of the substrates in this series, diol **172** included, were isolated as solids.



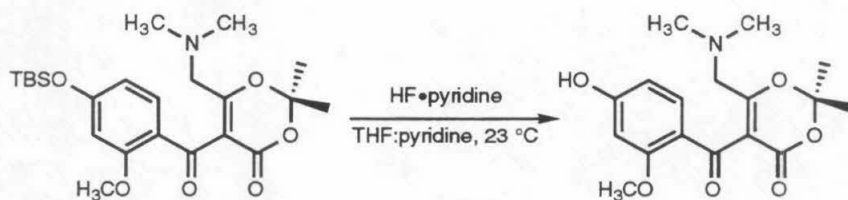
Oxidation of diol **172** to a 2,5-cyclohexadienone substrate was briefly pursued. Treatment of diol **172** with iodobenzene bis(trifluoroacetate) (2.1 equiv) in acetic acid gave 2-methoxy-1,4-benzoquinone as the major product. This product may form via oxidative

assistance from the benzylic alcohol. When this reaction (1.1 equiv oxidant) was performed in trifluoroethanol with excess sodium acetate (10.0 equiv), a multitude of unidentifiable polar products were produced.

**172**

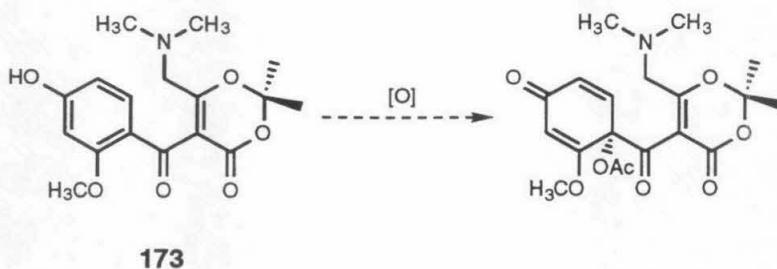
Efforts were then focused on the more advanced intermediate, ketone **171**. The desilylated ketone would appear to be an ideal starting material for phenol oxidation because of the lability of its methylene protons. In ketones **161** and **171**, the methylene protons are readily exchanged in deuterated solvent. Thus, an intramolecular cyclization on to the intermediate dienone may even occur in situ. The methylene protons of ketone **161** underwent deuterium exchange with methanol- $d_4$  (30.0 equiv) in  $CDCl_3$  (0.013 M) with a half-life of 10 h. In acetic acid- $d_6$ , however, this substrate was subject to ketal hydrolysis. Similarly, the methylene protons of ketone **171** displayed deuterium exchange with methanol- $d_4$  (30.0 equiv) in  $CDCl_3$  (0.014 M) with a half-life of 26 h. In acetic acid- $d_6$ , this exchange was very rapid ( $t_{1/2} < 5$  min). By comparison, the direct aldol adduct **170** showed absolutely no deuterium incorporation in acetic acid- $d_6$ .

Deprotection of the TBS ether of ketone **171** was accomplished with the HF•pyridine complex buffered with pyridine in THF. Similar to the deprotection of ketone **161**, phenol **173** was only isolated in low crude yield ( $\leq 50\%$ ). Phenol **173** was found to

**171****173**

be stable in acetic acid by  $^1\text{H}$  NMR analysis and underwent only minimal decomposition after 4 h.

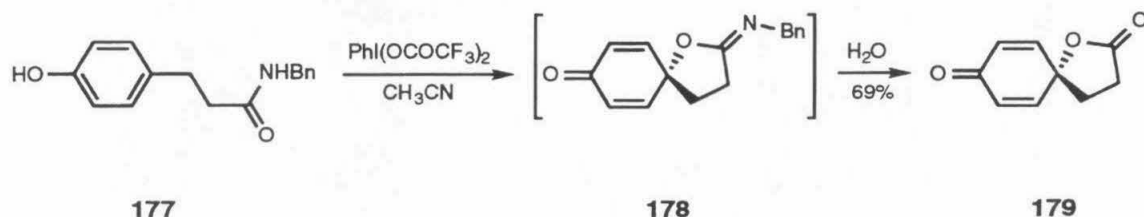
The *p*-oxidation of phenol **173** was then studied in depth using as reagents iodobenzene diacetate, iodobenzene bis(trifluoroacetate), lead(IV) acetate, and manganese(III) acetate. These oxidants were all used in excess (1.5–7 equiv). Experiments performed in solvents other than acetic acid were also performed in the presence of trifluoroacetic acid (1 equiv) to protonate the dimethylamino group prior to addition of the oxidant. The desired product was not observed in any of these reactions. 2-Methoxy-1,4-benzoquinone was produced when using iodobenzene bis(trifluoroacetate) as the oxidant. The most interesting results occurred when using iodobenzene diacetate in acetic acid and iodobenzene bis(trifluoroacetate) and dry sodium acetate (10 equiv) in trifluoroethanol. In these experiments, very polar compounds were produced that were extremely difficult to isolate due to their affinity for silica gel and their overall insolubility in most organic solvents.



In an effort to determine the nature of the polar products that were being formed, oxidation reactions of phenol **173** in acetic acid- $d_6$  were followed by  $^1\text{H}$  NMR. In the presence of iodobenzene bis(trifluoroacetate) (1.1 equiv), phenol **173** underwent complete conversion to an intermediate containing both of the starting materials. Although iodobenzene was then released, none of the desired product was observed. Instead, two singlets were observed in the aromatic region. Hydrolysis of the ketal from this intermediate was eventually observed.

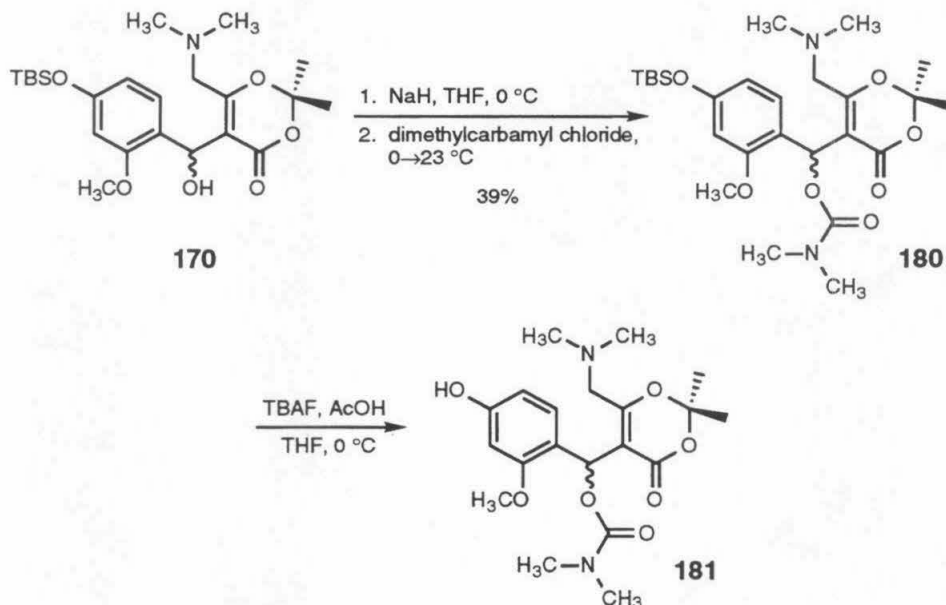


to determine whether oxidative spirolactonization could also occur from internal nucleophilic addition by a carbamate.

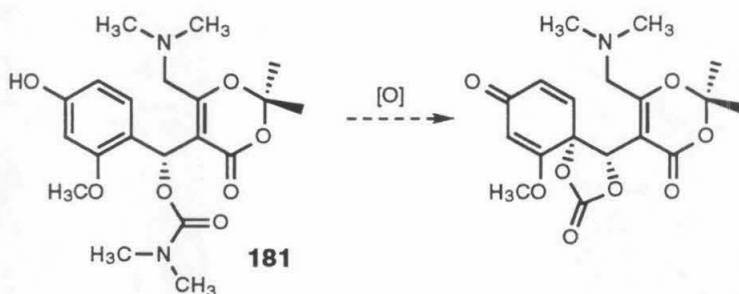


The synthesis of carbamate **181** was therefore pursued (Scheme XIX). Deprotonation of aldol adduct **170** with sodium hydride (5.5 equiv) in THF (0 °C) followed by acylation of the resulting alkoxide with dimethylcarbamyl chloride (10.0 equiv, 0→23 °C) provided carbamate **180** in 39% (unoptimized) yield along with 28% recovered starting material. Desilylation of the TBS aryl ether **180** with tetrabutylammonium fluoride (1.5 equiv) and acetic acid (3.5 equiv) in THF (0 °C) afforded the unstable phenol **181**, which was used in crude form in subsequent reactions.

### Scheme XIX



A few preliminary attempts were made at the oxidation of phenol **181** to the desired spirocyclohexadienone. Reaction of phenol **181** with iodobenzene bis(trifluoroacetate) (2.4 equiv) in trifluoroethanol resulted in the rapid decomposition of the starting material. The use of the milder oxidant iodobenzene diacetate (1.4 equiv) in trifluoroethanol provided similar results. Finally, the reaction course of phenol **181** was observed by  $^1\text{H}$  NMR in acetic acid- $d_6$  (the starting material was stable in this solvent). The addition of iodobenzene diacetate (1.2 equiv) resulted in significant and immediate decomposition of the starting material. Product formation was not observed. Although these preliminary results were not encouraging, this study of the oxidation of phenol **181** is not complete, and further experimentation is warranted.



## Conclusion

The research presented here has led to a concise strategy for the completion of the total synthesis of tetracycline. The left-hand half, phthalide **83**, has been prepared in 5 steps in 56% overall yield from commercially available starting material. Several isobenzofuran Diels–Alder reactions have been carried out in an effort to model the proposed condensation of the two halves of tetracycline. Specifically, a thermal Diels–Alder reaction has been shown to be successful with an enone dienophile containing a 1,3-dicarbonyl unit ( $\mathbf{84} + \mathbf{100} \rightarrow \mathbf{101} + \mathbf{102}$ ), proceeding with apparent *exo* selectivity. Dimethylamine **110** was prepared in 3 steps in 66% yield from 6-chloromethyl-2,2-dimethyl-1,3-dioxin-4-one as a protected, yet fully functionalized, right-hand half of the A ring of tetracycline. Several studies aimed at the annulation of amine **110** to a suitable B-

*ring precursor* to provide the proposed bicyclic right-hand half of tetracycline have been described. Finally, a novel and potentially rapid route to this right-hand half involving the preparation of intermediate 2,4-cyclohexadienones or 2,5-cyclohexadienones via oxidation of phenol precursors has been briefly examined. With further study, it is believed that this route will, in fact, lead to the elusive right-hand half and subsequently to completion of the total synthesis of tetracycline.

## Experimental Section

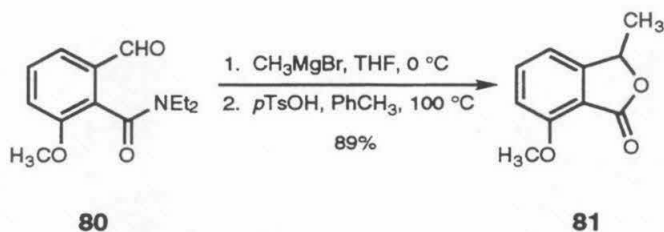
**General Procedures.** All reactions were performed in flame-dried round bottom or modified Schlenk (Kjeldahl shape) flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Where necessary (so noted), reaction mixtures were degassed by alternate evacuation/argon-flush cycles (five or more iterations). Organic solutions were concentrated by rotary evaporation at ~25 Torr (water aspirator). Flash chromatography was performed as described by Still et al.,<sup>33</sup> employing 230–400 mesh silica gel. Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel containing a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light and/or exposure to an acidic solution of *p*-anisaldehyde or ceric ammonium molybdate followed by heating on a hot plate.

**Materials.** Commercially available reagents were used as received with the following exceptions. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Benzene, toluene, dichloromethane, diisopropylamine, chlorotrimethylsilane, pyridine, and triethylamine were distilled from calcium hydride at 760 Torr. Methanol was distilled from magnesium at atmospheric pressure. Dimethylcarbonyl chloride, titanium(IV) isopropoxide, and benzaldehyde were distilled at 1 Torr. Anhydrous *N,N*-dimethylformamide was purchased from Aldrich Chemical Co. and was stored over 4Å molecular sieves. High purity 1,2-dichloroethane and acetic acid were stored over 4Å molecular sieves. The Dess–Martin periodinane<sup>96</sup> and dimethyldioxirane<sup>117</sup> were prepared according to literature procedures. The molarity of *n*-butyllithium solutions was determined using *N*-benzylidenebenzylamine as an indicator (average of three determinations).<sup>118</sup> Phase-separated 1:1 mixtures of chlorotrimethylsilane and triethylamine were prepared by the addition of equal volume amounts of each compound via syringe to a



15 mL Pyrex test tube fitted with a rubber septum and the subsequent centrifugation of the mixture for 30 min.

**Instrumentation.** Infrared (IR) spectra were obtained using a Perkin-Elmer 1600 FT-IR spectrophotometer internally referenced to a polystyrene standard. Data are presented as follows: frequency of absorption ( $\text{cm}^{-1}$ ), intensity of absorption (s = strong, m = medium, w = weak, br = broad), and assignment (where appropriate). Proton nuclear magnetic resonance ( $^1\text{H}$  NMR) and carbon nuclear magnetic resonance ( $^{13}\text{C}$  NMR) spectra were obtained on General Electric QE-300 (300 MHz) or JEOL JX-400 (400 MHz) NMR spectrometers; chemical shifts are expressed in parts per million ( $\delta$  scale) relative to an internal standard of chloroform ( $^1\text{H}$ , 7.26;  $^{13}\text{C}$ , 77.0), benzene- $d_5$  ( $^1\text{H}$ , 7.20;  $^{13}\text{C}$ , 128.0), methanol- $d_4$  ( $^{13}\text{C}$ , 44.9), acetone- $d_6$  ( $^{13}\text{C}$ , 29.8), or acetonitrile- $d_3$  ( $^{13}\text{C}$ , 1.3). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, ABq = AB quartet), integration, coupling constant in hertz (Hz), and assignment.  $^1\text{H}$  NMR difference nOe spectra of degassed samples were obtained on a Bruker AM-500 (500 MHz) NMR spectrometer. High resolution mass spectra (HRMS) were obtained at the University of California, Irvine Mass Spectrometry Facility.



Methylmagnesium bromide (30.0 mL of a 3.0 M solution in diethyl ether, 90.0 mmol, 2.1 equiv) was added to an ice-cooled solution of aldehyde **80** (10.3 g, 43.8 mmol, 1 equiv)<sup>75a</sup> in tetrahydrofuran (400 mL). The reaction mixture was stirred at 0 °C for 30 min. After stirring for 5 min at 23 °C, the reaction mixture was partitioned between saturated aqueous ammonium chloride solution (275 mL) and ethyl acetate (100 mL). The layers were separated, and the product was extracted with ethyl acetate (2 × 300 mL). The combined organics were dried over sodium sulfate and were concentrated. The crude solid was diluted with toluene (400 mL) at 23 °C. *p*-Toluenesulfonic acid monohydrate (9.17 g, 48.2 mmol, 1.1 equiv) was added, and the resulting solution was stirred at 100 °C for 2 h. The reaction mixture was cooled to 23 °C and was partitioned between water (300 mL) and ethyl acetate (100 mL). The layers were separated, and the product was extracted with ethyl acetate (2 × 300 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash chromatography (30–45% ethyl acetate–hexanes) to yield phthalide **81** (6.94 g, 89%) as a yellow oil.

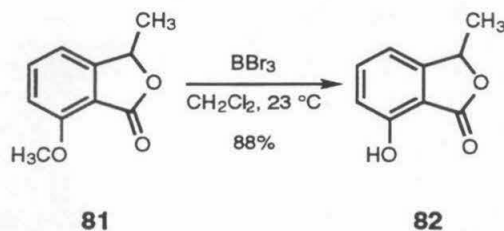
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>), δ: 7.56 (t, 1H, *J* = 7.8 Hz, aryl H (*m* to COCH<sub>3</sub>)), 6.91 (d, 1H, *J* = 7.3 Hz, aryl H), 6.88 (d, 1H, *J* = 8.3 Hz, aryl H), 5.41 (q, 1H, *J* = 6.6 Hz, CHCH<sub>3</sub>), 3.94 (s, 3H, OCH<sub>3</sub>), 1.54 (d, 3H, *J* = 6.6 Hz, CH<sub>3</sub>)

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>), δ: 168.2 (C=O), 158.3, 153.9, 136.1, 113.1, 113.0, 110.5, 76.3 (CHCH<sub>3</sub>), 55.8 (OCH<sub>3</sub>), 20.3 (CH<sub>3</sub>)

FTIR (neat),  $\text{cm}^{-1}$ : 2978 (m), 2931 (m), 1758 (s, C=O), 1605 (s),  
1488 (s), 1310 (s), 1284 (s), 1246 (s), 1204 (s),  
1081 (s), 1036 (s)

HRMS (EI): Calc'd for  $\text{C}_{10}\text{H}_{10}\text{O}_3$   $[\text{M}]^+$ : 178.0630  
Found: 178.0629

TLC (80% EtOAc in hexanes),  $R_f$ : 0.60



Boron tribromide (92 mL of a 1.0 M solution in  $\text{CH}_2\text{Cl}_2$ , 92.0 mmol, 2.4 equiv) was transferred via cannula into a cooled ( $-78\text{ }^\circ\text{C}$ ) solution of phthalide **81** (6.94 g, 38.9 mmol, 1 equiv) in dichloromethane (225 mL). Upon complete addition, the cold bath was removed and the reaction mixture was stirred at  $23\text{ }^\circ\text{C}$  for 105 min. The reaction mixture was partitioned between water (350 mL) and dichloromethane (100 mL). The layers were separated, and the product was extracted with dichloromethane ( $2 \times 200\text{ mL}$ ). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the crude mixture by flash chromatography (30% ethyl acetate–hexanes) provided 7-hydroxy-3-methylphthalide **82** (5.62 g, 88%) as a tan solid.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 7.54 (t, 1H,  $J = 7.8\text{ Hz}$ , aryl H (*m* to COTBS)), 6.91 (d, 1H,  $J = 8.3\text{ Hz}$ , aryl H), 6.90 (d, 1H,  $J = 7.4\text{ Hz}$ , aryl H), 5.57 (q, 1H,  $J = 6.7\text{ Hz}$ , CHCH<sub>3</sub>), 1.63 (d, 3H,  $J = 6.7\text{ Hz}$ , CH<sub>3</sub>)

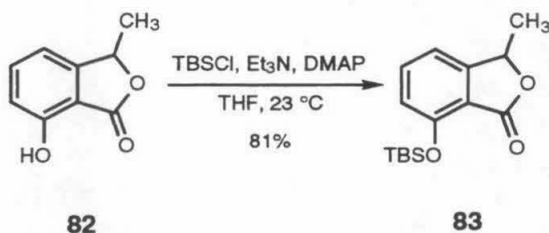
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 171.7 (C=O), 156.3, 151.4, 136.8, 115.2, 112.7, 110.7, 79.0 (CH(CH<sub>3</sub>)), 20.1 (CH<sub>3</sub>)

FTIR (neat),  $\text{cm}^{-1}$ : 3542 (m, OH), 3419 (br, OH), 2936 (w), 1724 (s, C=O), 1632 (m), 1606 (m), 1476 (m), 1306 (m), 1205 (m), 1095 (m), 1044 (m)

HRMS (EI): Calc'd for  $\text{C}_9\text{H}_8\text{O}_3$  [ $\text{M}$ ]<sup>+</sup>: 164.0473

Found: 164.0468

TLC (80% EtOAc in hexanes),  $R_f$ : 0.74



*tert*-Butyldimethylsilyl chloride (2.86 g, 19.0 mmol, 3.0 equiv) was added to a solution of 7-hydroxy-3-methylphthalide **82** (1.04 g, 6.33 mmol, 1 equiv) and triethylamine (3.50 mL, 25.3 mmol, 4.0 equiv) in tetrahydrofuran (25.0 mL) 23 °C. 4-Dimethylaminopyridine (77 mg, 633  $\mu$ mol, 0.1 equiv) was added to the reaction mixture and the resulting cloudy suspension was stirred for 110 min. The reaction mixture was poured into water (70 mL), and the product was extracted with ethyl acetate (3  $\times$  50 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash chromatography (5% ethyl acetate–hexanes) provided silyl-protected phthalide **83** as a white solid (1.43 g, 81% yield).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 7.48 (t, 1H,  $J$  = 7.8 Hz, aryl **H** (*m* to COTBS)), 6.94 (d, 1H,  $J$  = 7.6 Hz, aryl **H**), 6.81 (d, 1H,  $J$  = 8.1 Hz, aryl **H**), 5.39 (q, 1H,  $J$  = 6.6 Hz, **CHCH**<sub>3</sub>), 1.55 (d, 3H,  $J$  = 6.7 Hz, **CH**<sub>3</sub>), 1.02 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 0.25 (s, 6H,  $\text{Si}(\text{CH}_3)_2$ )

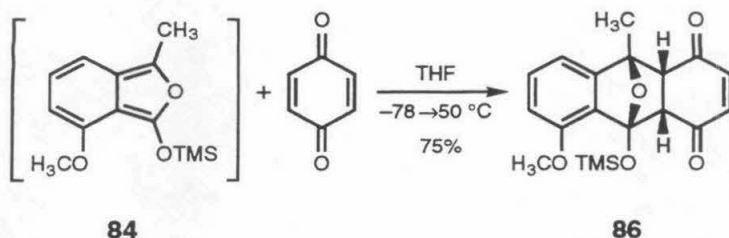
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 168.0 (**C=O**), 155.0, 153.6, 135.5, 120.1, 115.9, 113.9, 76.0 (**CHCH**<sub>3</sub>), 25.6 ( $\text{SiC}(\text{CH}_3)_3$ ), 20.6 (**CH**<sub>3</sub>), 18.4 ( $\text{SiC}(\text{CH}_3)_3$ ), −4.5 ( $\text{Si}(\text{CH}_3)_2$ )

FTIR (neat),  $\text{cm}^{-1}$ : 2932 (m), 2859 (m), 1768 (s, **C=O**), 1604 (s), 1481 (s), 1302 (s), 1256 (m), 1237 (m), 1200 (m), 1028 (s), 985 (s), 838 (s)

HRMS (EI): Calc'd for  $\text{C}_{14}\text{H}_{19}\text{O}_3\text{Si}$  [**M** − **CH**<sub>3</sub>]<sup>+</sup>: 263.1103

Found: 263.1097

TLC (20% EtOAc in hexanes),  $R_f$ : 0.49



Potassium bis(trimethylsilyl)amide (700  $\mu\text{L}$  of a 0.5 M solution in toluene, 350  $\mu\text{mol}$ , 1.3 equiv) was added via syringe to a degassed, chilled ( $-78^\circ\text{C}$ ) solution of phthalide **81** (52.8 mg, 280  $\mu\text{mol}$ , 1.1 equiv) in tetrahydrofuran (4.0 mL). The resulting bright yellow reaction mixture was stirred at  $-78^\circ\text{C}$  for 25 min, and then a 1:1 (v/v) mixture of chlorotrimethylsilane and triethylamine was added (240  $\mu\text{L}$ ,  $\sim 942$   $\mu\text{mol}$  TMSCl, 3.5 equiv). The reaction mixture was warmed to  $-20^\circ\text{C}$  and was stirred for 3.0 min, at which point the solution decolorized. After cooling to  $-78^\circ\text{C}$ , the reaction mixture was treated with 1,4-benzoquinone (29.1 mg, 269  $\mu\text{mol}$ , 1 equiv), and the reaction flask was transferred to an oil bath preheated to  $50^\circ\text{C}$ . After 10 min, the reaction mixture was cooled to  $23^\circ\text{C}$  and was poured into a half-saturated aqueous ammonium chloride solution (30 mL). The product was extracted from the aqueous layer with a 1:1 mixture of ethyl acetate and hexanes ( $3 \times 40$  mL). The combined organic layers were dried over sodium sulfate and were concentrated.  $^1\text{H}$  NMR ( $\text{C}_6\text{D}_6$ ) analysis of the crude reaction mixture using an internal standard (*trans*-1,2-dichloroethylene) indicated a 75% yield of the *endo* Diels–Alder adduct **86**. For characterization purposes, adduct **86** was purified by flash chromatography (20–30% ethyl acetate–hexanes) in low yield (26%).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 7.14 (t, 1H,  $J = 8.2$  Hz, aryl H (*m* to  $\text{COCH}_3$ )), 6.68 (d, 1H,  $J = 8.3$  Hz, aryl H (*o* to  $\text{COCH}_3$ )), 6.58 (d, 1H,  $J = 7.3$  Hz, aryl H (*p* to  $\text{COCH}_3$ )), 5.86 (ABq, 2H,  $J = 10.3$  Hz,  $\Delta\nu = 29.9$  Hz,  $\text{CH}=\text{CH}$ ), 3.77 (s, 3H,  $\text{OCH}_3$ ), 3.30 (ABq, 2H,

$J = 9.2 \text{ Hz}$ ,  $\Delta\nu = 19.7 \text{ Hz}$ , **CHCH**), 1.91 (s, 3H, **CH<sub>3</sub>**), 0.17 (s, 9H, **OSi(CH<sub>3</sub>)<sub>3</sub>**)

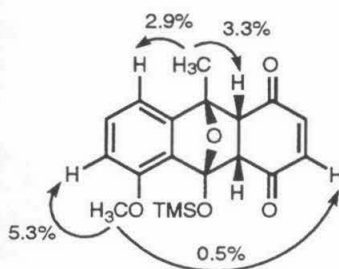
<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>),  $\delta$ : 195.9 (**C=O**), 193.6 (**C=O**), 154.2, 146.0, 138.9, 137.8, 130.4, 129.5, 112.0, 111.1, 109.8, 83.3 (**CCH<sub>3</sub>**), 57.0, 56.8, 55.4, 16.9 (**CH<sub>3</sub>**), 1.0 (**Si(CH<sub>3</sub>)<sub>3</sub>**)

FTIR (neat), cm<sup>-1</sup>: 2960 (w), 1676 (s, **C=O**), 1600 (m), 1484 (m), 1357 (s), 1307 (s), 1252 (m), 1173 (m), 1138 (m), 1048 (m), 844 (s)

HRMS (FAB): Calc'd for C<sub>19</sub>H<sub>23</sub>O<sub>5</sub>Si [**M + H**]<sup>+</sup>: 359.1315  
Found: 359.1305

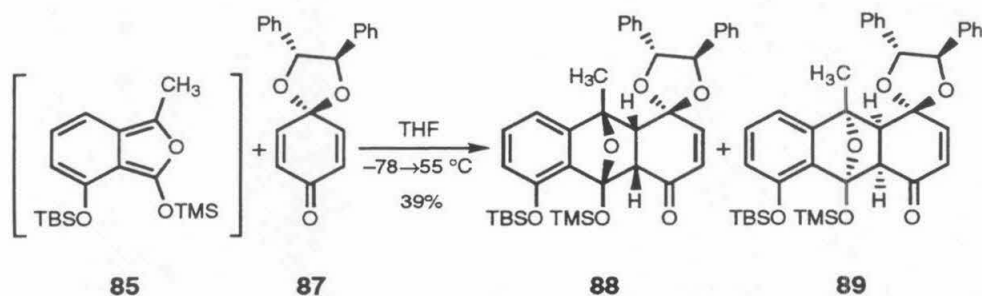
TLC (30% EtOAc in hexanes),  $R_f$ : 0.39

<sup>1</sup>H nOe difference spectra for **86** are summarized below (500 MHz, CDCl<sub>3</sub>):



**86**





Potassium bis(trimethylsilyl)amide (450  $\mu\text{L}$  of a 0.5 M solution in toluene, 225  $\mu\text{mol}$ , 1.2 equiv) was added via syringe to a degassed, cooled ( $-78\text{ }^{\circ}\text{C}$ ) solution of phthalide **83** (52.2 mg, 188  $\mu\text{mol}$ , 1 equiv) in tetrahydrofuran (2.5 mL). The bright orange reaction mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 30 min. A 1:1 (v/v) mixture of chlorotrimethylsilane in triethylamine (143  $\mu\text{L}$ ,  $\sim 563\text{ }\mu\text{mol}$  TMSCl, 3.0 equiv) was added. The reaction mixture was warmed to  $-20\text{ }^{\circ}\text{C}$  for 1.5 min, at which point the solution decolorized. The reaction mixture was cooled to  $-78\text{ }^{\circ}\text{C}$ , quinone monoketal **87** (69 mg, 225  $\mu\text{mol}$ , 1.2 equiv)<sup>79</sup> was added, and the reaction flask was immediately transferred to a pre-heated ( $55\text{ }^{\circ}\text{C}$ ) oil bath. After 1 h, the reaction mixture was cooled to  $23\text{ }^{\circ}\text{C}$ . A half-saturated aqueous sodium bicarbonate solution (5 mL) was added, and the product was extracted with ethyl acetate ( $3 \times 5\text{ mL}$ ). The combined organic layers were dried over sodium sulfate and were concentrated. Flash column chromatography of the residue (5–10% ethyl acetate–hexanes) provided the *endo* Diels–Alder adducts **88** and **89** (1:1 inseparable mixture of diastereomers, 48.3 mg, 39% yield) as colorless oils, along with quinone monoketal **87** (26.4 mg, 38%).

Diels–Alder adducts **88** and **89**:

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 7.31–7.42 (m, 12H, Ph), 7.20–7.28 (m, 8H, Ph), 6.96–7.09 (complex, 2H, aryl H (*m* to COTBS)), 6.84 (d, 1H,  $J = 7.0\text{ Hz}$ , aryl H), 6.74 (d, 1H,  $J = 7.2\text{ Hz}$ , aryl H), 6.59 (d, 1H,  $J = 8.1\text{ Hz}$ , aryl

**H**), 6.57 (d, 1H,  $J = 8.2$  Hz, aryl **H**), 6.03 (dd, 1H,  $J = 10.3, 1.5$  Hz, C(O)CH=CH), 5.89 (dd, 1H,  $J = 10.3, 1.5$  Hz, C(O)CH=CH), 5.30 (d, 1H,  $J = 10.2$  Hz, C(O)CH=CH), 5.27 (d, 1H,  $J = 10.2$  Hz, C(O)CH=CH), 4.96 (d, 1H,  $J = 8.7$  Hz, CHPh), 4.78 (d, 1H,  $J = 8.4$  Hz, CHPh), 4.66 (d, 1H,  $J = 8.9$  Hz, CHPh), 4.63 (d, 1H,  $J = 8.6$  Hz, CHPh), 3.40 (dd, 1H,  $J = 9.4, 1.6$  Hz, C(O)CH), 3.30 (d, 1H,  $J = 9.4$  Hz, C(O)CHCH), 3.27 (d, 1H,  $J = 8.1$  Hz, C(O)CHCH), 3.22 (dd, 1H,  $J = 8.1, 1.5$  Hz, C(O)CH), 2.05 (s, 3H, CH<sub>3</sub>), 1.94 (s, 3H, CH<sub>3</sub>), 1.04 (s, 18H, Si(CH<sub>3</sub>)<sub>3</sub>), 0.30 (s, 6H, Si(CH<sub>3</sub>)<sub>2</sub>), 0.27 (s, 6H, Si(CH<sub>3</sub>)<sub>2</sub>), 0.26 (s, 18H, Si(CH<sub>3</sub>)<sub>3</sub>)

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>),  $\delta$ :

194.0 (C=O), 193.4 (C=O), 150.1, 149.9, 146.9 (2C), 142.9, 141.3, 136.1, 135.8, 135.4, 134.9, 132.4, 132.3, 126.3–129.3 (complex, multiple C: 129.3, 129.2, 129.1, 129.0, 128.8, 128.7, 128.4, 128.0, 127.5, 126.9, 126.4, 126.3), 118.4 (2C), 113.3, 113.0, 109.5 (2C), 104.2, 103.6, 86.5, 86.4, 85.6, 84.2, 82.2, 81.9, 57.1, 56.9, 56.6, 56.1, 26.0 (2  $\times$  Si(CH<sub>3</sub>)<sub>3</sub>), 19.8 (CH<sub>3</sub>), 19.0 (CH<sub>3</sub>), 18.4 (2  $\times$  Si(CH<sub>3</sub>)<sub>3</sub>), 1.6 (2  $\times$  Si(CH<sub>3</sub>)<sub>3</sub>), -4.1 (2  $\times$  Si(CH<sub>3</sub>)<sub>2</sub>), -4.2 (2  $\times$  Si(CH<sub>3</sub>)<sub>2</sub>)

FTIR (neat), cm<sup>-1</sup>:

2931 (m), 2858 (w), 1679 (s, C=O), 1596 (m),

1477 (s), 1358 (m), 1313 (s), 1253 (s), 1124 (s),  
972 (s), 839 (s)

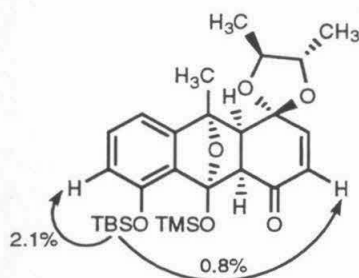
HRMS (CI):

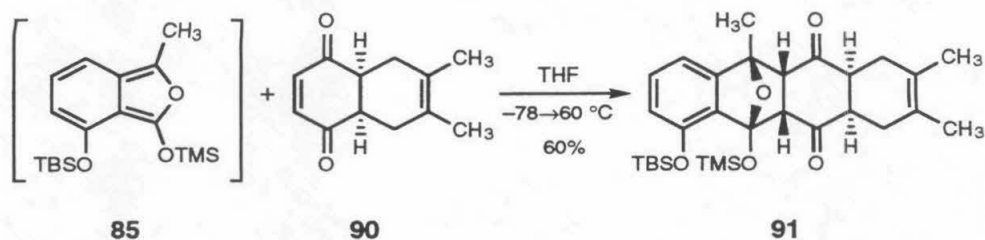
Calc'd for  $C_{38}H_{47}O_6Si_2$   $[M + H]^+$ : 655.2911

Found: 655.2908

TLC (30% EtOAc in hexanes),  $R_f$ : 0.72

$^1H$  nOe difference spectra for the following related adduct (~2:1 mixture of diastereomers) are summarized below (500 MHz,  $C_6D_6$ ):





Potassium bis(trimethylsilyl)amide (330  $\mu\text{L}$  of a 0.5 M solution in toluene, 164  $\mu\text{mol}$ , 1.6 equiv) was added via syringe to a degassed, cooled ( $-78^\circ\text{C}$ ) solution of phthalide **83** (43 mg, 154  $\mu\text{mol}$ , 1.5 equiv) in tetrahydrofuran (1.0 mL). The bright orange solution was stirred at  $-78^\circ\text{C}$  for 30 min. A 1:1 (v/v) mixture of chlorotrimethylsilane and triethylamine (115  $\mu\text{L}$ ,  $\sim 461$   $\mu\text{mol}$  TMSCl, 4.5 equiv) was added and the reaction mixture was warmed to  $-20^\circ\text{C}$  for 1.0 min, at which point the solution decolorized. After cooling the reaction mixture to  $-78^\circ\text{C}$ , a solution of enedione **90** (19.5 mg, 102  $\mu\text{mol}$ , 1 equiv)<sup>80</sup> in THF (0.5 mL) was added by syringe. The reaction flask was immediately transferred to an oil bath preheated to  $60^\circ\text{C}$ . After 70 min, the reaction mixture was cooled to  $23^\circ\text{C}$ . A half-saturated aqueous sodium bicarbonate solution (5 mL) was then added to the reaction mixture and the product was extracted with ethyl acetate ( $3 \times 5$  mL). The combined organic layers were dried over sodium sulfate and were concentrated. The crude oil was purified by flash chromatography (2% ethyl acetate–hexanes) to give the *endo* Diels–Alder adduct **91** (33.0 mg, 60%).

$^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ ),  $\delta$ : 6.88 (t, 1H, aryl H (*m* to COTBS)), 6.73 (d, 1H,  $J = 7.2$  Hz, aryl H (*o* to COTBS)), 6.63 (d, 1H,  $J = 8.1$  Hz, aryl H (*p* to COTBS)), 3.35 (d, 1H,  $J = 10.2$  Hz, C(O)CHCOTMS), 2.94 (d, 1H,  $J = 10.2$  Hz, C(O)CHCCH<sub>3</sub>), 2.27 (m, 1H, CH), 2.05 (s, 3H, CH<sub>3</sub>), 1.80–1.96 (complex, 3H, CH), 1.35–1.52 (complex, 2H, CH), 1.42 (s,

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ :

3H,  $\text{CH}_3\text{C}=\text{CCH}_3$ ), 1.35 (s, 3H,  $\text{CH}_3\text{C}=\text{CCH}_3$ ),  
1.17 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 0.46 (s, 9H,  $\text{Si}(\text{CH}_3)_3$ ),  
0.40 (s, 3H,  $\text{Si}(\text{CH}_3)_2$ ), 0.25 (s, 3H,  $\text{Si}(\text{CH}_3)_2$ )  
208.1 (C=O), 204.0 (C=O), 150.0, 147.4,  
131.8, 129.5, 123.6, 122.1, 118.5, 112.6,  
109.6, 82.4 (CCH<sub>3</sub>), 58.0, 57.8, 48.3, 44.6,  
29.7, 29.0, 25.9 ( $\text{SiC}(\text{CH}_3)_3$ ), 18.9, 18.7, 18.3,  
18.1, 1.4 ( $\text{Si}(\text{CH}_3)_3$ ), -4.1 ( $\text{Si}(\text{CH}_3)_2$ ), -4.4  
( $\text{Si}(\text{CH}_3)_2$ )

FTIR (neat),  $\text{cm}^{-1}$ :

2930 (m), 2859 (m), 1708 (s, C=O), 1596 (m),  
1478 (s), 1355 (m), 1315 (s), 1252 (s), 992 (m),  
845 (s)

HRMS (FAB):

Calc'd for  $\text{C}_{30}\text{H}_{45}\text{O}_5\text{Si}_2$   $[\text{M} + \text{H}]^+$ : 541.2805

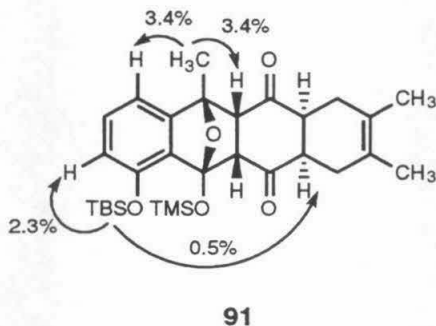
Found: 541.2801

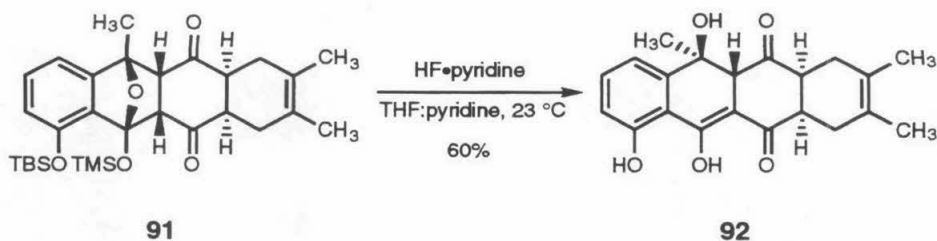
TLC (1:2:7 EtOAc:PhCH<sub>3</sub>:hexane),

$R_f$ :

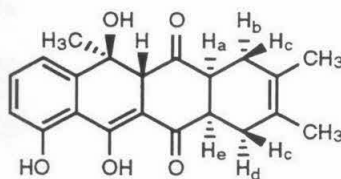
0.53

$^1\text{H}$  nOe difference spectra for **91** are summarized below (500 MHz,  $\text{C}_6\text{D}_6$ ):





A solution of hydrogen fluoride•pyridine buffered in pyridine was prepared at 0 °C by the addition of 70% hydrogen fluoride•pyridine (1.0 mL) to a solution of pyridine (4.0 mL) in THF (10.0 mL).<sup>76</sup> A 200  $\mu\text{L}$ -aliquot was added to an ice-cooled solution of adduct **91** (33.0 mg, 61.0  $\mu\text{mol}$ , 1 equiv) in tetrahydrofuran (2.0 mL). The reaction mixture was stirred at 23 °C. After 1 h, another 200  $\mu\text{L}$ -aliquot of hydrogen fluoride•pyridine solution was added. The reaction mixture was poured into water (5 mL) after 2 h and the product was extracted with ethyl acetate (3  $\times$  5 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Flash chromatography purification of the residue (10–20% ethyl acetate–hexanes) provided tetracyclic compound **92** (13 mg, 60%) as a yellow solid.



$^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ ),  $\delta$ : 15.06 (s, 1H, enol **H**), 12.31 (s, 1H, phenol **H**), 7.51 (d, 1H,  $J = 7.7$  Hz, aryl **H** ( $p$  to COH)), 7.16 (t, 1H,  $J = 7.9$  Hz, aryl **H** ( $m$  to COH)), 6.93 (d, 1H,  $J = 7.9$  Hz, aryl **H** ( $o$  to COH)), 5.14 (s, 1H, OH), 3.12 (s, 1H,  $\text{CHC}(\text{OH})\text{CH}_3$ ), 2.59 (d, 1H,  $J = 16.9$  Hz, **H<sub>b</sub>**), 2.49 (m, 1H, **H<sub>e</sub>**), 2.05 (m, 1H, **H<sub>a</sub>**), 1.90 (dd, 1H,  $J = 16.5, 4.9$  Hz, **H<sub>d</sub>**), 1.38–1.59 (complex, 2H, **H<sub>c</sub>**), 1.52 (s,

3H,  $\text{CH}_3\text{C}=\text{CCH}_3$ ), 1.38 (s, 3H,  $\text{CH}_3\text{C}=\text{CCH}_3$ ),  
1.10 (s, 3H,  $\text{CH}_3$ )

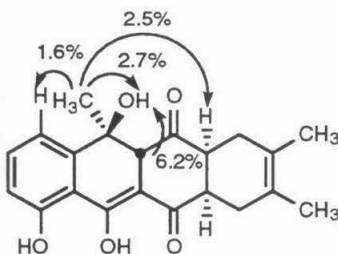
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 213.0 (C=O), 191.9 (C=O), 181.9 (C=O),  
161.9, 148.7, 137.2, 124.1, 122.3, 116.8,  
115.0, 112.9, 101.1, 72.8, 52.1, 47.7, 39.0,  
32.0, 28.2, 27.6, 18.9 (2C)

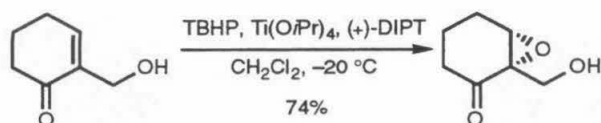
FTIR (neat),  $\text{cm}^{-1}$ : 3457 (br, OH), 2922 (w), 1698 (w, C=O), 1614  
(s), 1583 (s), 1454 (m), 1363 (m), 1312 (m),  
1243 (m), 1206 (m), 1160 (m)

HRMS (FAB): Calc'd for  $\text{C}_{21}\text{H}_{23}\text{O}_5$   $[\text{M} + \text{H}]^+$ : 355.1545  
Found: 355.1539

TLC (20% EtOAc in hexanes),  $R_f$ : 0.40

$^1\text{H}$  nOe difference spectra for **92** are summarized below (500 MHz,  $\text{C}_6\text{D}_6$ ):



**94**

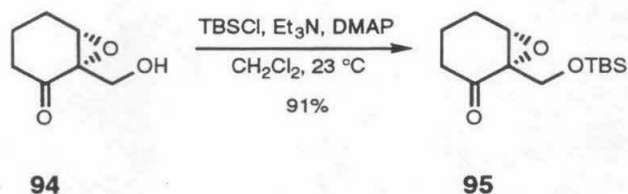
Titanium(IV) isopropoxide (17.2 mL, 58.3 mmol, 5.0 equiv) was added to a degassed, cooled ( $-20\text{ }^\circ\text{C}$ ) solution of diisopropyl L-tartrate (14.7 mL, 69.9 mmol, 6.0 equiv) and crushed, activated 4Å molecular sieves (441 mg, 30% wt/wt) in dichloromethane (110 mL). 2-(Hydroxymethyl)-2-cyclohexen-1-one (1.47 g, 11.7 mmol, 1 equiv)<sup>81</sup> was added to the reaction mixture by syringe in a dichloromethane solution ( $2 \times 5.0\text{ mL}$  portions), and the resulting reaction mixture was stirred for 30 min at  $-20\text{ }^\circ\text{C}$ . *tert*-Butyl hydroperoxide (TBHP, 14.6 mL of a 4.0 M solution in  $\text{CH}_2\text{Cl}_2$ , 58.3 mmol, 5.0 equiv) was added dropwise to the reaction mixture over a period of 20 min. To drive the reaction to completion, more TBHP (7.3 mL, 29.2 mmol, 2.5 equiv) was added after 13.5 h. After 15 h, the reaction mixture was removed from the cooling bath, a solution of 10% aqueous tartaric acid (100 mL) was added, and the resulting solution was stirred vigorously at  $23\text{ }^\circ\text{C}$ . The mixture was filtered through a pad of Celite and rinsed with water (200 mL) and dichloromethane (250 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (200 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Flash chromatography (40–50% ethyl acetate–hexanes) of the crude oil provided the chiral epoxide **94** as a pale yellow oil (1.23 g, 74%).

Acylation of epoxide **94** (20.1 mg, 141  $\mu\text{mol}$ , 1 equiv) proceeded with optically-pure  $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetic acid chloride ( $\sim 353\text{ } \mu\text{mol}$ , 2.5 equiv), triethylamine (79  $\mu\text{L}$ , 566  $\mu\text{mol}$ , 4.0 equiv), and 4-dimethylaminopyridine (cat.) in dichloromethane (2.0 mL) at  $23\text{ }^\circ\text{C}$  for 4 h. Analysis of the purified Mosher ester derivative by  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) established that epoxide **94** was of  $\geq 94\%$  ee.<sup>83,84</sup> The Mosher acid chloride ( $\sim 353\text{ } \mu\text{mol}$ , 2.5 equiv) was prepared in situ from chiral  $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetic acid (83.0 mg, 353  $\mu\text{mol}$ , 2.5 equiv), oxalyl



chloride (49  $\mu\text{L}$ , 566  $\mu\text{mol}$ , 4.0 equiv), and *N,N*-dimethylformamide (2.0  $\mu\text{L}$ , 26  $\mu\text{mol}$ , 0.18 equiv) in dichloromethane (1.0 mL), followed by removal of the excess oxalyl chloride and solvent at reduced pressure (1 Torr).

|   |   |
|---|---|
| $^1\text{H}$ NMR (300 MHz, $\text{CDCl}_3$ ), $\delta$ :    | 3.86 (m, 2H, $\text{CH}_2\text{OH}$ ), 3.62 (br t, 1H, epoxide <b>H</b> ), 2.55 (dt, 1H, $J = 16.9, 4.7$ Hz, $\text{C}(\text{O})\text{CH}_2$ ), 2.42 (t, 1H, $J = 6.6$ Hz, $\text{CH}_2\text{OH}$ ), 2.22–2.29 (m, 1H, $\text{C}(\text{O})\text{CH}_2$ ), 1.62–2.13 (complex, 4H, $\text{CH}_2$ ) |
| $^{13}\text{C}$ NMR (100 MHz, $\text{CDCl}_3$ ), $\delta$ : | 207.6 ( $\text{C}=\text{O}$ ), 60.6 (quaternary epoxide <b>C</b> ), 60.5, 59.9, 36.9, 23.0, 17.6  |
| FTIR (neat), $\text{cm}^{-1}$ :                             | 3415 (br, OH), 2948 (m), 1704 (s, $\text{C}=\text{O}$ ), 1432 (w), 1351 (w), 1101 (w), 1047 (m), 879 (w)  |
| HRMS (EI):  | Calc'd for $\text{C}_7\text{H}_9\text{O}_3$ $[\text{M} - \text{H}]^+$ : 141.0552<br>Found: 141.0554   |
| TLC (EtOAc), $R_f$ :  | 0.56  |



Triethylamine (2.5 mL, 17.9 mmol, 2.5 equiv) was added to an ice-cooled solution of *tert*-butyldimethylsilyl chloride (2.16 g, 14.4 mmol, 2.0 equiv) and epoxide **94** (1.02 g, 7.18 mmol, 1 equiv) in dichloromethane (40 mL). 4-Dimethylaminopyridine (219 mg, 1.79 mmol, 0.25 equiv) was added and the reaction mixture was stirred at 23 °C for 3 h. The reaction mixture was poured into water (60 mL) and the product was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash chromatography (3–5% ethyl acetate–hexanes) gave TBS-protected epoxide **95** (1.67 g, 91%) as a colorless oil.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 4.03 (ABq, 2H,  $J = 12.4$  Hz,  $\Delta\nu = 92.6$  Hz,  $\text{CH}_2\text{OTBS}$ ), 3.70 (br t, 1H, epoxide H), 2.56 (dt, 1H,  $J = 15.9, 4.5$  Hz,  $\text{C(O)CH}_2$ ), 2.20–2.25 (m, 1H,  $\text{C(O)CH}_2$ ), 1.60–2.07 (complex, 4H,  $\text{CH}_2$ ), 0.87 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 0.05 (s, 6H,  $\text{Si}(\text{CH}_3)_2$ )

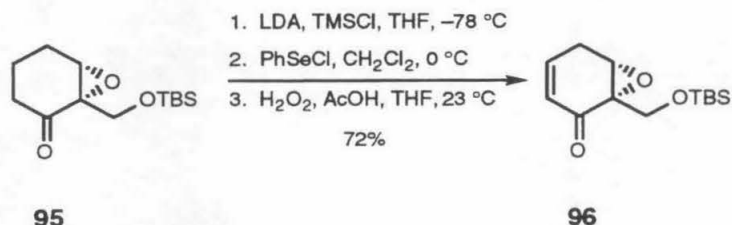
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 205.3 (C=O), 60.5 (quaternary epoxide C), 58.5, 57.7, 36.7, 25.5 ( $\text{SiC}(\text{CH}_3)_3$ ), 22.8, 17.9, 17.3, –5.8 ( $\text{Si}(\text{CH}_3)_2$ ), –5.9 ( $\text{Si}(\text{CH}_3)_2$ )

FTIR (neat),  $\text{cm}^{-1}$ : 2931 (s), 2857 (m), 1710 (s, C=O), 1463 (m), 1393 (w), 1255 (m), 1134 (m), 1068 (m), 875 (m), 839 (s), 780 (m)

HRMS (CI): Calc'd for  $\text{C}_{13}\text{H}_{25}\text{O}_3\text{Si}$   $[\text{M} + \text{H}]^+$ : 257.1573

Found: 257.1569

TLC (40% EtOAc in hexanes),  $R_f$ : 0.81



*n*-Butyllithium (1.17 mL of a 2.52 M solution in hexanes, 2.95 mmol, 1.50 equiv) was added to a degassed, cooled ( $-78\text{ }^\circ\text{C}$ ) solution of diisopropylamine (420  $\mu\text{L}$ , 2.99 mmol, 1.52 equiv) in tetrahydrofuran (8.5 mL). The resulting solution was stirred at  $0\text{ }^\circ\text{C}$  for 10 min and was then cooled to  $-78\text{ }^\circ\text{C}$ . Chlorotrimethylsilane (750  $\mu\text{L}$ , 5.90 mmol, 3.0 equiv) was added to the reaction mixture, followed by the dropwise addition of a solution of ketone **95** (504 mg, 1.97 mmol, 1 equiv) in THF (1.5 mL). After 45 min, the reaction mixture was quenched with the addition of triethylamine (825  $\mu\text{L}$ , 5.92 mmol, 3.0 equiv) and was poured into saturated aqueous sodium bicarbonate solution (10 mL). The aqueous layer was extracted with a 1:1 mixture of ethyl acetate and hexanes ( $3 \times 8\text{ mL}$ ). The combined organic layers were dried over sodium sulfate and were concentrated.

The resulting crude oil was dissolved in dichloromethane (5.0 mL) and was cooled to  $0\text{ }^\circ\text{C}$ . Phenylselenenyl chloride (418 mg, 2.18 mmol, 1.1 equiv) was added and the reaction mixture was stirred at  $0\text{ }^\circ\text{C}$ . After 15 min, a 1:9 mixture of saturated aqueous sodium bicarbonate solution and water (10 mL) was added to the reaction mixture, which was then stirred at  $23\text{ }^\circ\text{C}$ . The layers were separated, and the aqueous layer was further extracted with a 1:1 mixture of ethyl acetate and hexanes ( $2 \times 10\text{ mL}$ ). The combined organic layers were dried over sodium sulfate and were concentrated.

The resulting crude oil was diluted with tetrahydrofuran (10.0 mL) and was cooled to  $0\text{ }^\circ\text{C}$ . Acetic acid (23  $\mu\text{L}$ , 394  $\mu\text{mol}$ , 0.2 equiv) and hydrogen peroxide (469 mg of a 30% (w/w) aqueous solution, 4.14 mmol, 2.1 equiv) were added sequentially to the reaction mixture, which was then stirred vigorously at  $23\text{ }^\circ\text{C}$ . After 15 min, the reaction mixture was diluted with a 1:9 mixture of saturated aqueous sodium bicarbonate solution and water (10 mL), brine (2 mL), and ethyl acetate (8 mL). The layers were separated, and

the aqueous layer was further extracted with ethyl acetate ( $2 \times 10$  mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the crude oil by flash chromatography (5–10% ethyl acetate–hexanes) provided enone **96** as a tan oil (361 mg, 72%).

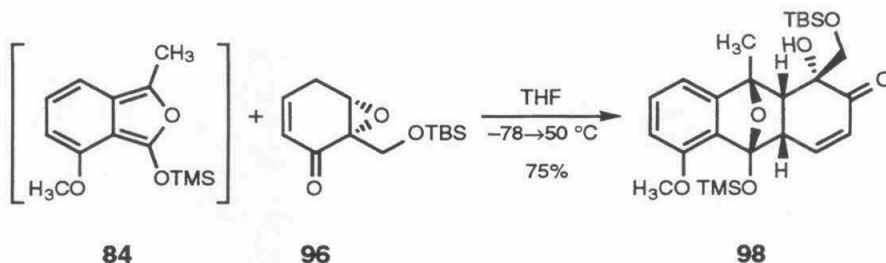
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 6.52 (dm, 1H,  $J = 10.6$  Hz,  $\text{C}(\text{O})\text{CH}=\text{CH}$ ), 5.93 (dt, 1H,  $J = 10.6, 2.0$  Hz,  $\text{C}(\text{O})\text{CH}$ ), 4.08 (ABq, 2H,  $J = 12.6$  Hz,  $\Delta\nu = 80.7$  Hz,  $\text{CH}_2\text{OTBS}$ ), 3.82 (br t, 1H, epoxide **H**), 2.92 (dd, 1H,  $J = 21.6, 4.4$  Hz,  $\text{CH}_2$ ), 2.68 (dq, 1H,  $J = 21.4, 2.5$  Hz,  $\text{CH}_2$ ), 0.83 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 0.02 (s, 6H,  $\text{Si}(\text{CH}_3)_2$ )

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 195.0 ( $\text{C}=\text{O}$ ), 143.2 ( $\text{C}(\text{O})\text{CH}=\text{CH}$ ), 126.8 ( $\text{C}(\text{O})\text{CH}$ ), 60.3 (quaternary epoxide **C**), 58.1, 54.8, 27.3, 25.7 ( $\text{SiC}(\text{CH}_3)_3$ ), 18.1 ( $\text{SiC}(\text{CH}_3)_3$ ),  $-5.5$  ( $\text{Si}(\text{CH}_3)_2$ ),  $-5.6$  ( $\text{Si}(\text{CH}_3)_2$ )

FTIR (neat),  $\text{cm}^{-1}$ : 2931 (m), 2857 (m), 1679 (s,  $\text{C}=\text{O}$ ), 1470 (w), 1407 (m), 1256 (m), 1141 (m), 1082 (s), 837 (s), 780 (m)

HRMS (CI): Calc'd for  $\text{C}_{13}\text{H}_{23}\text{O}_3\text{Si}$  [ $\text{M} + \text{H}$ ] $^+$ : 255.1416  
Found: 255.1417

TLC (10% EtOAc in hexanes),  $R_f$ : 0.22



Potassium bis(trimethylsilyl)amide (430  $\mu\text{L}$  of a 0.5 M solution in toluene, 214  $\mu\text{mol}$ , 5.5 equiv) was added to a degassed, chilled ( $-78\text{ }^{\circ}\text{C}$ ) solution of phthalide **81** (36.1 mg, 203  $\mu\text{mol}$ , 5.2 equiv) in tetrahydrofuran (2.5 mL). The resulting bright yellow solution was stirred at  $-78\text{ }^{\circ}\text{C}$  for 25 min, at which point a 1:1.6 (v/v) mixture of chlorotrimethylsilane and triethylamine (85  $\mu\text{L}$ ,  $\sim 250\text{ }\mu\text{mol}$  TMSCl, 13.0 equiv) was added. The reaction mixture was warmed to  $-20\text{ }^{\circ}\text{C}$  for 6.0 min (solution decolorized) and was then cooled to  $-78\text{ }^{\circ}\text{C}$ . Enone **96** (10 mg, 39  $\mu\text{mol}$ , 1 equiv) was added to the reaction mixture in a tetrahydrofuran solution (0.5 mL). The reaction flask was immediately transferred to an oil bath preheated to  $50\text{ }^{\circ}\text{C}$ . After 40 min, the reaction mixture was concentrated in vacuo and then partitioned between a half-saturated aqueous sodium bicarbonate solution (40 mL) and a 1:1 mixture of ethyl acetate and hexanes (50 mL). The layers were separated and the aqueous layer was further extracted with a 1:1 mixture of ethyl acetate in hexanes (50 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Flash chromatography of the residue (5% ethyl acetate–hexanes) provided the *endo* Diels-Alder adduct **98** (15 mg) in 75% yield.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 7.09 (t, 1H,  $J = 8.2\text{ Hz}$ , aryl H (*m* to  $\text{COCH}_3$ )), 6.84 (dd, 1H,  $J = 10.1, 4.8\text{ Hz}$ ,  $\text{C}(\text{O})\text{CH}=\text{CH}$ ), 6.75 (d, 1H,  $J = 7.3\text{ Hz}$ , aryl H (*p* to  $\text{COCH}_3$ )), 6.63 (d, 1H,  $J = 8.2\text{ Hz}$ , aryl H (*o* to  $\text{COCH}_3$ )), 5.63 (dd, 1H,  $J = 10.2, 1.2\text{ Hz}$ ,  $\text{C}(\text{O})\text{CH}$ ), 3.75 (s, 3H,  $\text{OCH}_3$ ), 3.69 (s, 1H, OH), 3.43 (ABq,

2H,  $J = 9.8$  Hz,  $\Delta\nu = 17.4$  Hz,  $\text{CH}_2\text{OTBS}$ ), 3.25 (m, 1H,  $\text{CHCOTMS}$ ), 2.74 (d, 1H,  $J = 8.9$  Hz,  $\text{CHCCH}_3$ ), 1.87 (s, 3H,  $\text{CH}_3$ ), 0.77 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 0.13 (s, 9H,  $\text{Si}(\text{CH}_3)_3$ ),  $-0.06$  (s, 3H,  $\text{Si}(\text{CH}_3)_2$ ),  $-0.08$  (s, 3H,  $\text{Si}(\text{CH}_3)_2$ )

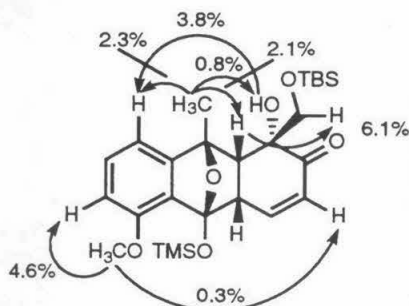
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 195.7 ( $\text{C}=\text{O}$ ), 154.3, 147.4, 145.8, 129.3, 129.2, 127.0, 113.8, 111.3, 109.9, 82.8, 78.0, 72.2, 55.0, 51.5, 50.1, 25.7 ( $\text{SiC}(\text{CH}_3)_3$ ), 19.3, 18.1, 1.0 ( $\text{Si}(\text{CH}_3)_3$ ),  $-5.5$  ( $\text{Si}(\text{CH}_3)_2$ ),  $-5.6$  ( $\text{Si}(\text{CH}_3)_2$ )

FTIR (neat),  $\text{cm}^{-1}$ : 3459 (w, OH), 2932 (m), 2857 (m), 1693 (m,  $\text{C}=\text{O}$ ), 1599 (m), 1484 (m), 1309 (s), 1252 (s), 1131 (m), 1053 (m), 987 (w), 840 (s), 757 (m)

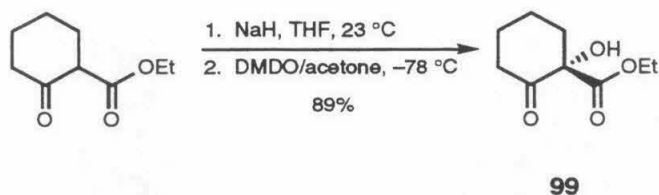
HRMS (FAB): Calc'd for  $\text{C}_{26}\text{H}_{41}\text{O}_6\text{Si}_2$   $[\text{M} + \text{H}]^+$ : 505.2441  
Found: 505.2446

TLC (30% EtOAc in hexanes),  $R_f$ : 0.79

$^1\text{H}$  nOe difference spectra for **98** are summarized below (500 MHz,  $\text{CDCl}_3$ ):



**98**



Ethyl 2-cyclohexanonecarboxylate (150  $\mu\text{L}$ , 938  $\mu\text{mol}$ , 1 equiv) was added to a suspension of sodium hydride (43.1 mg of a 60% dispersion in mineral oil, 1.03  $\mu\text{mol}$ , 1.1 equiv) in tetrahydrofuran (10.0 mL) at 23  $^{\circ}\text{C}$ . After 10 min, the reaction mixture was cooled to  $-78\text{ }^{\circ}\text{C}$  and a solution of dimethyldioxirane (DMDO, 17.0 mL of a 0.086 M solution in acetone, 1.46  $\mu\text{mol}$ , 1.6 equiv) was added. The reaction mixture was quenched after 30 min upon addition of a pH 7 phosphate buffer (10 mL) and was warmed to 23  $^{\circ}\text{C}$ . The reaction mixture was poured into water (50 mL) and the product was extracted with ethyl acetate ( $3 \times 60\text{ mL}$ ). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash chromatography (10% ethyl acetate–hexanes) provided alcohol **99** (156 mg, 89%) as a colorless oil.

$^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ ),  $\delta$ : 4.60 (s, 1H, OH), 3.94 (m, 2H,  $\text{OCH}_2\text{CH}_3$ ), 2.64 (m, 1H,  $\text{CH}_2$ ), 2.44 (dt, 1H,  $J = 13.8, 4.6$  Hz,  $\text{CH}_2$ ), 2.24 (m, 1H,  $\text{CH}_2$ ), 1.38–1.55 (complex, 4H,  $\text{CH}_2$ ), 1.21 (m, 1H,  $\text{CH}_2$ ), 0.90 (t, 3H,  $J = 7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ )

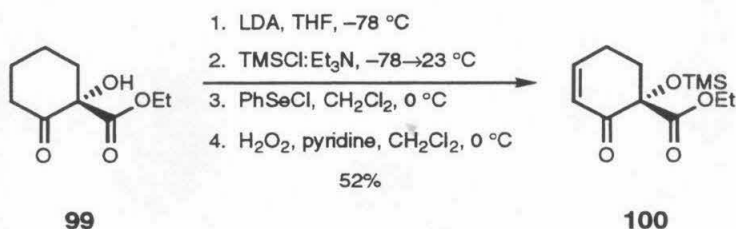
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 207.2 (C=O), 170.0 ( $\text{CO}_2\text{Et}$ ), 80.6 (COH), 62.0 ( $\text{OCH}_2\text{CH}_3$ ), 38.8, 37.6, 27.0, 21.9, 13.9

FTIR (neat),  $\text{cm}^{-1}$ : 3458 (br, OH), 2944 (m), 1721 (s, C=O), 1450 (w), 1368 (w), 1250 (s), 1211 (m), 1115 (m), 1018 (m)

HRMS (EI): Calc'd for  $\text{C}_9\text{H}_{14}\text{O}_4$   $[\text{M}]^+$ : 186.0892

Found: 186.0894

TLC (20% EtOAc in hexanes),  $R_f$ : 0.32



*n*-Butyllithium (250  $\mu\text{L}$  of a 2.37 M solution in hexanes, 590  $\mu\text{mol}$ , 2.2 equiv) was added to a degassed, cooled ( $-78\text{ }^{\circ}\text{C}$ ) solution of diisopropylamine (80  $\mu\text{L}$ , 620  $\mu\text{mol}$ , 2.3 equiv) in tetrahydrofuran (3 mL). The resulting solution was warmed to  $0\text{ }^{\circ}\text{C}$  for 10 min and was cooled to  $-78\text{ }^{\circ}\text{C}$ . A solution of alcohol **99** (50 mg, 270  $\mu\text{mol}$ , 1 equiv) in THF (0.5 mL) was added to the reaction mixture. After 65 min, the reaction mixture was quenched upon addition of a 1:1 (v/v) mixture of chlorotrimethylsilane and triethylamine (205  $\mu\text{L}$ ,  $\sim 810\text{ } \mu\text{mol}$  TMSCl, 3.0 equiv). After 5 min, the reaction mixture was allowed to warm slowly to  $23\text{ }^{\circ}\text{C}$  over 45 min. The reaction mixture was poured into a 1:9 mixture of saturated aqueous sodium bicarbonate solution and water (10 mL), and the product was extracted with a 1:1 mixture of ethyl acetate and hexanes ( $3 \times 25\text{ mL}$ ). The combined organic layers were dried over sodium sulfate and were concentrated.

A solution of the resulting crude oil in dichloromethane (2.5 mL) was cooled to  $0\text{ }^{\circ}\text{C}$ . Phenylselenenyl chloride (62 mg, 320  $\mu\text{mol}$ , 1.2 equiv) in dichloromethane (0.5 mL) was added to the reaction mixture. After 20 min, the reaction mixture was diluted with a 1:9 mixture of saturated aqueous sodium bicarbonate solution and water (4 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 mL) and was warmed to  $23\text{ }^{\circ}\text{C}$ . The layers were separated and the organic layer was washed with a 1:9 mixture of saturated aqueous sodium bicarbonate solution and water (4 mL). The organic layer was dried over sodium sulfate and was concentrated.

The crude  $\alpha$ -selenide was diluted with dichloromethane (2.0 mL) and was cooled to  $0\text{ }^{\circ}\text{C}$ . Pyridine (39  $\mu\text{L}$ , 540  $\mu\text{mol}$ , 2.0 equiv) and a solution of hydrogen peroxide (94 mg of a 30% (w/w) aqueous solution, 830  $\mu\text{mol}$ , 3.1 equiv) in water (2 mL) were added sequentially to the reaction mixture. After 40 min, the reaction mixture was warmed to  $23\text{ }^{\circ}\text{C}$ .



°C. The reaction mixture was then poured into saturated aqueous sodium bicarbonate solution (7 mL), and the product was extracted with dichloromethane ( $3 \times 5$  mL). The combined organic layers were washed with water (5 mL), dried over sodium sulfate, and were concentrated. Flash chromatography of the crude oil (5% ethyl acetate–hexanes) afforded enone **100** (36 mg, 52%) as a pale yellow oil.

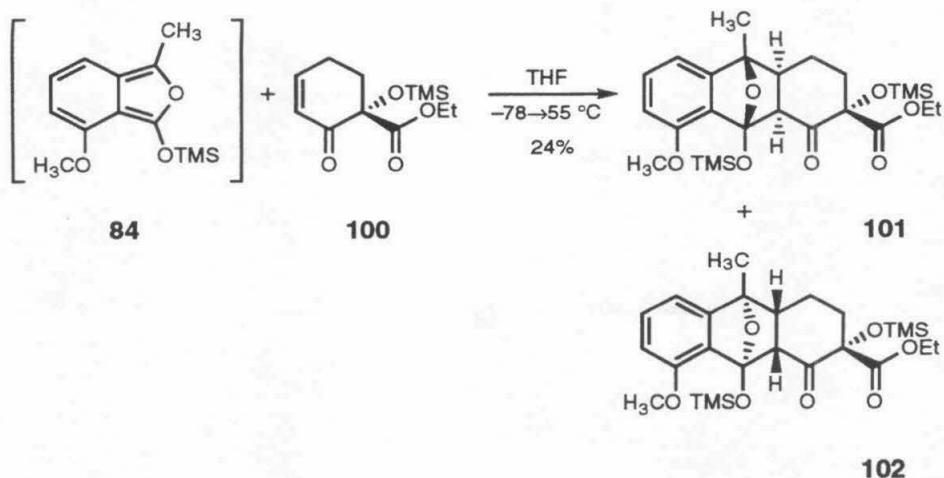
$^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ ),  $\delta$ : 6.17 (dt, 1H,  $J = 10.2, 3.8$  Hz,  $\text{C(O)CH=CH}$ ), 5.95 (dt, 1H,  $J = 10.2, 1.9$  Hz,  $\text{C(O)CH}$ ), 3.95 (q, 2H,  $J = 7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 2.38 (m, 1H,  $\text{CH}_2$ ), 1.75–2.00 (complex, 3H,  $\text{CH}_2$ ), 0.92 (t, 3H,  $J = 7.2$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 0.44 (s, 9H,  $\text{Si(CH}_3)_3$ )

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 194.3 ( $\text{C=O}$ ), 171.0 ( $\text{CO}_2\text{Et}$ ), 150.1 ( $\text{C(O)CH=CH}$ ), 127.9 ( $\text{C(O)CH}$ ), 80.3 ( $\text{COTMS}$ ), 61.4, 35.0, 23.6, 13.9, 1.6 ( $\text{Si(CH}_3)_3$ )

FTIR (neat),  $\text{cm}^{-1}$ : 2958 (m), 1754 (s,  $\text{C=O}$ ), 1694 (s,  $\text{C=O}$ ), 1388 (m), 1249 (s), 1180 (s), 1130 (s), 898 (m), 846 (s)

HRMS (CI): Calc'd for  $\text{C}_{12}\text{H}_{21}\text{O}_4\text{Si}$  [ $\text{M} + \text{H}$ ] $^+$ : 257.1209  
Found: 257.1202

TLC (20% EtOAc in hexanes),  $R_f$ : 0.50



Potassium bis(trimethylsilyl)amide (410  $\mu\text{L}$  of a 0.5 M solution in toluene, 206  $\mu\text{mol}$ , 1.4 equiv) was added to a degassed, chilled ( $-78^\circ\text{C}$ ) solution of phthalide **81** (34.1 mg, 191  $\mu\text{mol}$ , 1.3 equiv) in tetrahydrofuran (2.0 mL). The resulting bright yellow solution was stirred at  $-78^\circ\text{C}$  for 35 min. A 1:1 (v/v) mixture of chlorotrimethylsilane and triethylamine (170  $\mu\text{L}$ ,  $\sim 662$   $\mu\text{mol}$  TMSCl, 4.5 equiv) was added and the reaction mixture was warmed to  $-20^\circ\text{C}$  for 1 min, at which point the solution decolorized. The reaction mixture was cooled to  $-78^\circ\text{C}$ , and a solution of enone **100** (37.7 mg, 147  $\mu\text{mol}$ , 1 equiv) in tetrahydrofuran (500  $\mu\text{L}$ ) was added. The reaction flask was transferred to a pre-heated ( $55^\circ\text{C}$ ) oil bath for 65 min. The cooled reaction mixture was diluted with a half-saturated aqueous sodium bicarbonate solution (5 mL), and the product was extracted with ethyl acetate ( $3 \times 5$  mL). The combined organic layers were dried over sodium sulfate and were concentrated. Flash chromatography (2–5% ethyl acetate–hexanes) of the residue provided the *exo* Diels–Alder adduct **101** (11.0 mg, 15%), the *exo* Diels–Alder adduct **102** (7.0 mg, 9%), and the enone **100** (16.5 mg, 44%). Adduct **102** was contaminated with a minor amount of the apparent *endo* Diels–Alder diastereomeric adducts.

Major adduct **101**:

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 7.17 (dd, 1H,  $J = 8.1, 7.4$  Hz, aryl H (*m* to  $\text{COCH}_3$ ), 6.77 (d, 1H,  $J = 7.3$  Hz, aryl H), 6.72 (d, 1H,  $J = 8.2$  Hz, aryl H), 4.23 (q, 2H,  $J = 7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 3.86 (s, 3H,  $\text{OCH}_3$ ), 2.54 (m, 1H,  $\text{CH}_2$ ), 2.50 (d, 1H,  $J = 8.4$  Hz,  $\text{C}(\text{O})\text{CH}$ ), 2.38 (m, 1H,  $\text{CH}_2$ ), 2.10 (m, 1H,  $\text{CH}_2$ ), 1.96 (d, 1H,  $J = 7.3$  Hz,  $\text{C}(\text{O})\text{CHCH}$ ), 1.93 (m, 1H,  $\text{CH}_2$ ), 1.73 (s, 3H,  $\text{CH}_3$ ), 1.30 (t, 3H,  $J = 7.2$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 0.13 (s, 9H,  $\text{Si}(\text{CH}_3)_3$ ), 0.12 (s, 9H,  $\text{Si}(\text{CH}_3)_3$ )

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 206.4 ( $\text{C}=\text{O}$ ), 172.0 ( $\text{CO}_2\text{Et}$ ), 152.5, 151.2, 132.5, 129.2, 110.2 (2C), 108.9, 82.2, 80.6, 61.5, 56.4, 55.3, 43.4, 32.6, 17.4, 15.6, 14.1, 1.7 ( $\text{Si}(\text{CH}_3)_3$ ), 0.8 ( $\text{Si}(\text{CH}_3)_3$ )

FTIR (neat),  $\text{cm}^{-1}$ : 2958 (m), 1754 (m,  $\text{C}=\text{O}$ ), 1709 (w,  $\text{C}=\text{O}$ ), 1600 (w), 1483 (m), 1314 (m), 1250 (s), 1152 (m), 1054 (m), 845 (s)

HRMS (FAB): Calc'd for  $\text{C}_{25}\text{H}_{39}\text{O}_7\text{Si}_2$   $[\text{M} + \text{H}]^+$ : 507.2234

Found: 507.2229

TLC (20% EtOAc in hexanes),  $R_f$ : 0.61

Minor adduct **102**:

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 7.17 (t, 1H,  $J = 7.8$  Hz, aryl H (*m* to  $\text{COCH}_3$ ), 6.75 (d, 1H,  $J = 7.4$  Hz, aryl H), 6.72 (d, 1H,  $J = 8.4$  Hz, aryl H), 4.17 (q, 2H,  $J = 7.5$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 3.86 (s, 3H,  $\text{OCH}_3$ ), 2.54 (d, 1H,  $J$

= 8.3 Hz, C(O)CH), 2.41 (q, 1H,  $J = 7.2$  Hz, CH<sub>2</sub>), 2.24 (m, 2H, C(O)CHCH, CH<sub>2</sub>), 2.08 (m, 1H, CH<sub>2</sub>), 1.79 (m, 1H, CH<sub>2</sub>), 1.70 (s, 3H, CH<sub>3</sub>), 1.23 (t, 3H,  $J = 7.6$  Hz, OCH<sub>2</sub>CH<sub>3</sub>), 0.20 (s, 9H, Si(CH<sub>3</sub>)<sub>3</sub>), 0.13 (s, 9H, Si(CH<sub>3</sub>)<sub>3</sub>)

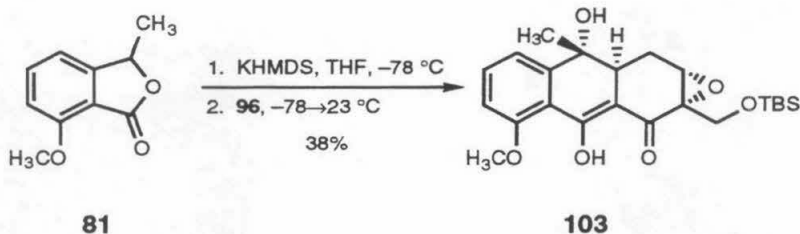
<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>),  $\delta$ : 205.2 (C=O), 172.7 (CO<sub>2</sub>Et), 152.8, 151.5, 131.9, 129.3, 110.1, 110.0, 108.8, 82.3, 80.7, 61.4, 56.9, 55.3, 44.0, 33.4, 18.4, 16.1, 14.0, 2.1 (Si(CH<sub>3</sub>)<sub>3</sub>), 0.8 (Si(CH<sub>3</sub>)<sub>3</sub>)

FTIR (neat), cm<sup>-1</sup>: 2958 (w), 1753 (m, C=O), 1716 (w, C=O), 1599 (w), 1483 (m), 1312 (m), 1249 (s), 1174 (m), 1053 (m), 844 (s)

HRMS (FAB): Calc'd for C<sub>25</sub>H<sub>39</sub>O<sub>7</sub>Si<sub>2</sub> [M + H]<sup>+</sup>: 507.2234

Found: 507.2229

TLC (20% EtOAc in hexanes),  $R_f$ : 0.51



Potassium bis(trimethylsilyl)amide (405  $\mu\text{L}$  of a 0.5 M solution in toluene, 200  $\mu\text{mol}$ , 5.2 equiv) was added to a degassed, chilled ( $-78\text{ }^{\circ}\text{C}$ ) solution of phthalide **81** (34.9 mg, 196  $\mu\text{mol}$ , 5.0 equiv) in tetrahydrofuran (2.5 mL). The resulting bright yellow solution was stirred for 25 min at  $-78\text{ }^{\circ}\text{C}$ , at which point a solution of enone **96** (10 mg, 39  $\mu\text{mol}$ , 1 equiv) in tetrahydrofuran (0.5 mL) was added. The reaction mixture was allowed to warm to  $23\text{ }^{\circ}\text{C}$ . After 55 min, the reaction mixture was quenched with the addition of a pH 7 phosphate buffer (4 mL), water (2 mL), and dichloromethane (5 mL). The layers were separated, and the aqueous layer was further extracted with dichloromethane ( $2 \times 6\text{ mL}$ ). The combined organic layers were dried over sodium sulfate and were concentrated. Flash chromatography (20–25% ethyl acetate–hexanes) of the residue gave the tricyclic product **103** (6.4 mg, 38%) as a tan oil.

$^1\text{H}$  NMR (400 MHz,  $\text{C}_6\text{D}_6$ ),  $\delta$ : 17.14 (s, 1H, enol **H**), 7.26 (dd, 1H,  $J = 7.8, 1.0$  Hz, aryl **H**), 7.14 (t, 1H,  $J = 8.0$  Hz, aryl **H** (*m* to  $\text{COCH}_3$ ), 6.41 (d, 1H,  $J = 7.8$  Hz, aryl **H**), 4.43 (ABq, 2H,  $J = 12.7$  Hz,  $\Delta\nu = 97.2$  Hz,  $\text{CH}_2\text{OTBS}$ ), 3.85 (d, 1H,  $J = 3.5$  Hz, epoxide **H**), 3.36 (s, 3H,  $\text{OCH}_3$ ), 2.77 (dd, 1H,  $J = 12.0, 6.0$  Hz,  $\text{CHC}(\text{OH})\text{CH}_3$ ), 2.18 (dm, 1H,  $J = 14.6$  Hz,  $\text{CH}_2$ ), 1.46 (dd, 1H,  $J = 14.2, 12.2$  Hz,  $\text{CH}_2$ ), 1.02 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 1.01 (s, 3H,  $\text{CH}_3$ ), 0.14 (s, 3H,  $\text{Si}(\text{CH}_3)_2$ ), 0.12 (s, 3H,

Si(CH<sub>3</sub>)<sub>2</sub>)

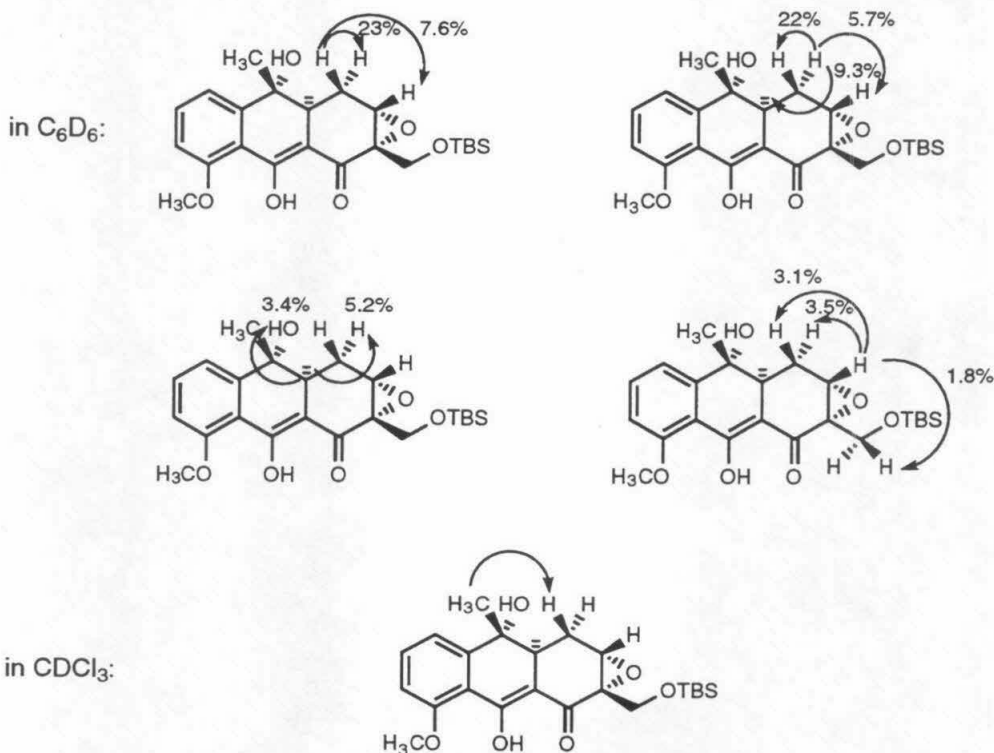
<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>), δ: 187.8 (C=O), 179.2 (C=O), 159.5, 151.7, 134.4, 117.0, 115.1, 111.5, 105.3, 73.1, 58.3, 58.2, 58.1, 56.3, 39.0, 25.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 24.1, 21.8, 18.4, -5.3 (Si(CH<sub>3</sub>)<sub>2</sub>), -5.4 (Si(CH<sub>3</sub>)<sub>2</sub>)

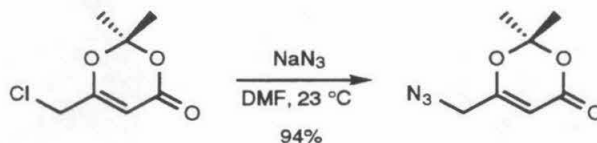
FTIR (neat), cm<sup>-1</sup>: 3466 (br, OH), 2930 (m), 2856 (w), 1595 (s, C=O), 1470 (m), 1337 (m), 1268 (s), 1127 (m), 1046 (m), 839 (s)

HRMS (FAB): Calc'd for C<sub>23</sub>H<sub>33</sub>O<sub>6</sub>Si [M + H]<sup>+</sup>: 433.2046  
Found: 433.2043

TLC (30% EtOAc in hexanes), *R<sub>f</sub>*: 0.64

<sup>1</sup>H nOe difference spectra for **103** are summarized below (500 MHz):



**111**

Sodium azide (486 mg, 7.47 mmol, 1.1 equiv) was added to a solution of 6-chloromethyl-2,2-dimethyl-1,3-dioxin-4-one (1.84 g, 10.4 mmol, 1 equiv)<sup>91</sup> in *N,N*-dimethylformamide (5.0 mL) at 23 °C. The reaction mixture was stirred for 35 min and was then poured into water (50 mL). The product was extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash chromatography (20% ethyl acetate–hexanes) provided azide **111** (1.17 g) in 94% yield as a pale yellow oil.

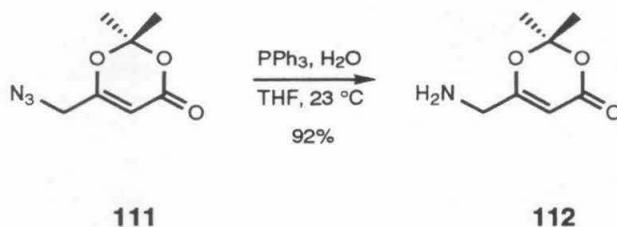
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), δ: 5.46 (s, 1H, C(O)CH), 3.86 (s, 2H, CH<sub>2</sub>N<sub>3</sub>), 1.70 (s, 6H, CH<sub>3</sub>)

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>), δ: 164.7 (C(O)CH=C), 160.0 (C=O), 107.4 (C(CH<sub>3</sub>)<sub>2</sub>), 94.6 (C(O)CH), 50.6 (CH<sub>2</sub>N<sub>3</sub>), 24.8 (CH<sub>3</sub>)

FTIR (neat), cm<sup>-1</sup>: 3000 (w), 2109 (s, N<sub>3</sub>), 1732 (s, C=O), 1643 (m), 1392 (m), 1273 (m), 1204 (m), 1018 (m), 902 (m), 812 (m)

HRMS (EI): Calc'd for C<sub>7</sub>H<sub>9</sub>N<sub>3</sub>O<sub>3</sub> [M]<sup>+</sup>: 183.0644  
Found: 183.0644

TLC (30% EtOAc in hexanes), *R*<sub>f</sub>: 0.64



Triphenylphosphine (1.84 g, 7.03 mmol, 1.1 equiv) was slowly added in two portions to a solution of azide **111** (1.17 g, 6.39 mmol, 1 equiv) in tetrahydrofuran (5.0 mL). After 5 min, water (175  $\mu\text{L}$ , 9.58 mmol, 1.5 equiv) was added to the reaction mixture. The reaction mixture was stirred at 23  $^\circ\text{C}$  for 36 h and was then concentrated in vacuo. Flash chromatography (3% methanol–dichloromethane) of the crude oil afforded amine **112** (918 mg, 92%) as an orange oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 5.42 (s, 1H,  $\text{C}(\text{O})\text{CH}$ ), 3.37 (s, 2H,  $\text{CH}_2\text{NH}_2$ ), 1.65 (s, 6H,  $\text{CH}_3$ ), 1.34 (br s, 2H,  $\text{NH}_2$ )

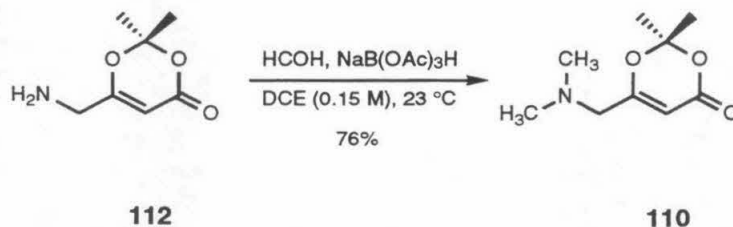
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 171.8 ( $\text{C}(\text{O})\text{CH}=\text{C}$ ), 161.1 ( $\text{C}=\text{O}$ ), 106.6 ( $\text{C}(\text{CH}_3)_2$ ), 91.8 ( $\text{C}(\text{O})\text{CH}$ ), 43.5 ( $\text{CH}_2\text{NH}_2$ ), 24.9 ( $\text{CH}_3$ )

FTIR (neat),  $\text{cm}^{-1}$ : 3382 (br,  $\text{NH}_2$ ), 2999 (w), 1726 (s,  $\text{C}=\text{O}$ ), 1635 (m), 1393 (m), 1274 (m), 1205 (m), 1010 (m), 904 (w), 810 (w)

HRMS (CI): Calc'd for  $\text{C}_7\text{H}_{12}\text{NO}_3$   $[\text{M} + \text{H}]^+$ : 158.0817  
Found: 158.0821

TLC (10%  $\text{CH}_3\text{OH}$  in  $\text{CH}_2\text{Cl}_2$ ),  $R_f$ : 0.29





Sodium triacetoxymethylborohydride (4.95 g, 23.4 mmol, 4.0 equiv) and formaldehyde (1.75 g of a 37% (w/w) aqueous solution, 17.5 mmol, 3.0 equiv) were added sequentially to a solution of amine **112** (918 mg, 5.84 mmol, 1 equiv) in 1,2-dichloroethane (40.0 mL) at 23 °C (it was important to keep the reaction mixture at a concentration of  $\leq 0.15$  M). After 45 min, the reaction mixture was poured into saturated aqueous sodium bicarbonate solution (30 mL), and the product was extracted with dichloromethane ( $3 \times 30$  mL). The combined organic layers were dried over sodium sulfate and were concentrated. Flash chromatography of the crude oil (30% ethyl acetate–hexanes with 1% triethylamine) gave dimethylamine **110** (822 mg, 76%) as a pale yellow solid. The  $^{13}\text{C}$  NMR spectral assignments were confirmed by an APT experiment.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 5.43 (s, 1H,  $\text{C}(\text{O})\text{CH}$ ), 3.00 (s, 2H,  $\text{CH}_2\text{N}(\text{CH}_3)_2$ ), 2.27 (s, 6H,  $\text{N}(\text{CH}_3)_2$ ), 1.68 (s, 6H,  $\text{CH}_3$ )

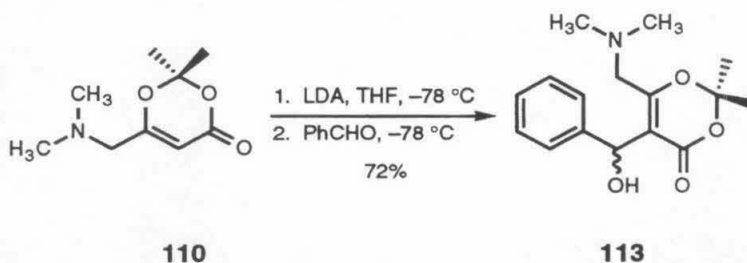
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 168.5 ( $\text{C}(\text{O})\text{CH}=\text{C}$ ), 161.0 ( $\text{C}=\text{O}$ ), 106.7 ( $\text{C}(\text{CH}_3)_2$ ), 94.6 ( $\text{C}(\text{O})\text{CH}$ ), 60.7 ( $\text{CH}_2\text{N}(\text{CH}_3)_2$ ), 45.5 ( $\text{N}(\text{CH}_3)_2$ ), 25.0 ( $\text{CH}_3$ )

FTIR (neat),  $\text{cm}^{-1}$ : 2947 (w), 2778 (w), 1731 (s,  $\text{C}=\text{O}$ ), 1637 (m), 1392 (m), 1275 (m), 1204 (m), 1012 (m), 902 (w), 811 (m)

HRMS (EI): Calc'd for  $\text{C}_9\text{H}_{15}\text{NO}_3$   $[\text{M}]^+$ : 185.1052

Found: 185.1051

TLC (80% EtOAc in hexanes),  $R_f$ : 0.12



*n*-Butyllithium (220  $\mu\text{L}$  of a 1.25 M solution in hexanes, 277  $\mu\text{mol}$ , 2.20 equiv) was added to a degassed, cooled ( $-78\text{ }^\circ\text{C}$ ) solution of diisopropylamine (40  $\mu\text{L}$ , 283  $\mu\text{mol}$ , 2.25 equiv) in tetrahydrofuran (1.0 mL). The resulting solution was warmed to  $0\text{ }^\circ\text{C}$  for 10 min and was then cooled to  $-78\text{ }^\circ\text{C}$ . A solution of amine **110** (48.9 mg, 264  $\mu\text{mol}$ , 2.1 equiv) in THF (500  $\mu\text{L}$ ) was added to the reaction mixture. After 35 min, benzaldehyde (13  $\mu\text{L}$ , 126  $\mu\text{mol}$ , 1 equiv) was added via syringe. After 20 min, the reaction mixture was quenched with water (5 mL) and was warmed to  $23\text{ }^\circ\text{C}$ . The product was extracted with ethyl acetate ( $3 \times 5\text{ mL}$ ). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash chromatography (70–80% ethyl acetate–hexanes) provided the aldol adduct **113** (26.3 mg, 72%) as a colorless oil. The  $^{13}\text{C}$  NMR spectral assignments were confirmed by an APT experiment.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 7.40 (d, 2H,  $J = 7.6\text{ Hz}$ , *o*-aryl H), 7.32 (t, 2H,  $J = 7.4\text{ Hz}$ , *m*-aryl H), 7.23 (d, 1H,  $J = 7.2\text{ Hz}$ , *p*-aryl H), 6.02 (s, 1H, CHOH), 2.70 (ABq, 2H,  $J = 13.3\text{ Hz}$ ,  $\Delta\nu = 155.8\text{ Hz}$ ,  $\text{CH}_2\text{N}(\text{CH}_3)_2$ ), 2.21 (s, 6H,  $\text{N}(\text{CH}_3)_2$ ), 1.72 (s, 3H,  $\text{CH}_3$ ), 1.67 (s, 3H,  $\text{CH}_3$ )

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 165.1 (C(O)C=C), 161.8 (C=O), 143.8, 128.1 (2 aryl CH), 126.8, 125.2 (2 aryl CH), 113.3 (C(O)C), 105.7 (C(CH<sub>3</sub>)<sub>2</sub>), 67.0 (CHOH), 59.5 (CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>), 44.8 (N(CH<sub>3</sub>)<sub>2</sub>), 25.4 (CH<sub>3</sub>),

25.1 (CH<sub>3</sub>)FTIR (neat), cm<sup>-1</sup>:

3422 (w, OH), 2940 (w), 1726 (s, C=O), 1623  
(m), 1391 (m), 1273 (m), 1202 (m), 1016 (m),  
701 (m)

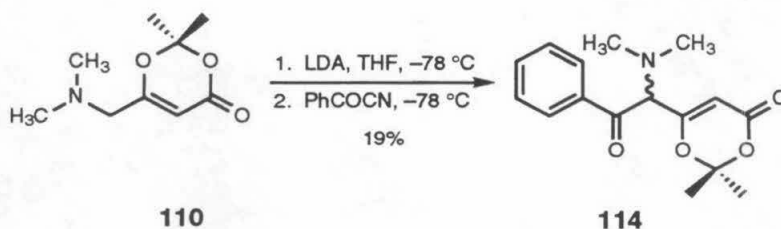
HRMS (CI):

Calc'd for C<sub>16</sub>H<sub>22</sub>NO<sub>4</sub> [M + H]<sup>+</sup>: 292.1549

Found: 292.1542

TLC (EtOAc), *R<sub>f</sub>*:

0.40



*n*-Butyllithium (123  $\mu\text{L}$  of a 1.48 M solution in hexanes, 182  $\mu\text{mol}$ , 1.30 equiv) was added to a degassed, cooled ( $-78^\circ\text{C}$ ) solution of diisopropylamine (26  $\mu\text{L}$ , 189  $\mu\text{mol}$ , 1.35 equiv) in tetrahydrofuran (1.0 mL). The resulting solution was warmed to  $0^\circ\text{C}$  for 10 min and was then cooled to  $-78^\circ\text{C}$ . A solution of amine **110** (31.1 mg, 168  $\mu\text{mol}$ , 1.2 equiv) in THF (500  $\mu\text{L}$ ) was added to the reaction mixture. After 60 min, a solution of benzoyl cyanide (18 mg, 140  $\mu\text{mol}$ , 1 equiv) in tetrahydrofuran (500  $\mu\text{L}$ ) was added. After an additional 20 min, the reaction mixture was quenched upon addition of water (5 mL) and was warmed to  $23^\circ\text{C}$ . The product was extracted with ethyl acetate ( $3 \times 5$  mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash chromatography (40% ethyl acetate–hexanes) gave the aldol adduct **114** (7.6 mg, 19%).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 8.02 (d, 2H,  $J = 7.9$  Hz, *o*-aryl H), 7.60 (t, 1H,  $J = 7.4$  Hz, *p*-aryl H), 7.47 (t, 2H,  $J = 7.6$  Hz, *m*-aryl H), 5.58 (s, 1H,  $\text{C}(\text{O})\text{CH}=\text{C}$ ), 4.54 (s, 1H,  $\text{CHN}(\text{CH}_3)_2$ ), 2.44 (s, 6H,  $\text{N}(\text{CH}_3)_2$ ), 1.59 (s, 3H,  $\text{CH}_3$ ), 1.54 (s, 3H,  $\text{CH}_3$ )

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 193.9 ( $\text{C}=\text{O}$ ), 165.9 ( $\text{C}(\text{O})\text{CH}=\text{C}$ ), 160.5 ( $\text{CO}_2\text{R}$ ), 136.0 (aryl C), 133.8 (aryl CH), 128.7 (4 aryl CH), 107.3 ( $\text{C}(\text{CH}_3)_2$ ), 97.2 ( $\text{C}(\text{O})\text{CH}=\text{C}$ ), 73.0 ( $\text{CHN}(\text{CH}_3)_2$ ), 43.1 ( $\text{N}(\text{CH}_3)_2$ ), 25.0 ( $\text{CH}_3$ ), 24.8 ( $\text{CH}_3$ )

FTIR (neat),  $\text{cm}^{-1}$ :

2945 (w), 1730 (s, C=O), 1627 (m), 1391 (m),  
1272 (m), 1204 (m), 1015 (m), 693 (m)

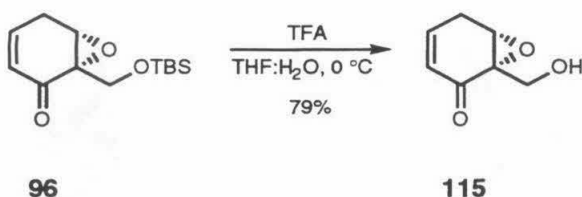
HRMS (CI):

Calc'd for  $\text{C}_{16}\text{H}_{20}\text{NO}_4$   $[\text{M} + \text{H}]^+$ : 290.1392

Found: 290.1390

TLC (EtOAc),  $R_f$ :

0.70



Trifluoroacetic acid (66  $\mu\text{L}$ , 852  $\mu\text{mol}$ , 2.5 equiv) was added to an ice-cooled solution of enone **96** (86.7 mg, 341  $\mu\text{mol}$ , 1 equiv) in a 1:1 mixture of tetrahydrofuran in water (4.0 mL). After 2.3 h, the reaction mixture was diluted with water (4 mL) and the product was extracted with dichloromethane ( $3 \times 5$  mL). The combined organic layers were dried over sodium sulfate and were concentrated. Flash chromatography of the residue (60% ethyl acetate–hexanes) provided the deprotected enone **115** (38.0 mg, 79%) as a volatile, colorless oil.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 6.59 (d(quintet), 1H,  $J = 10.4, 2.4$  Hz,  $\text{C(O)CH=CH}$ ), 6.02 (dt, 1H,  $J = 10.5, 1.9$  Hz,  $\text{C(O)CH}$ ), 3.98 (s, 2H,  $\text{CH}_2\text{OH}$ ), 3.80 (br s, 1H, epoxide H), 3.00 (dd, 1H,  $J = 21.4, 4.7$  Hz,  $\text{CH}_2$ ), 2.75 (dq, 1H,  $J = 21.4, 2.6$  Hz,  $\text{CH}_2$ ), 2.35 (br, 1H,  $\text{CH}_2\text{OH}$ )

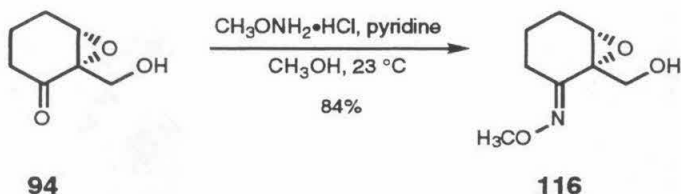
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 195.8 ( $\text{C=O}$ ), 143.7 ( $\text{C(O)CH=CH}$ ), 126.9 ( $\text{C(O)CH}$ ), 60.1, 59.8 (quaternary epoxide C), 56.6, 27.5

FTIR (neat),  $\text{cm}^{-1}$ : 3418 (br, OH), 2932 (w), 1669 (s,  $\text{C=O}$ ), 1404 (m), 1057 (m), 847 (m)

HRMS (CI): Calc'd for  $\text{C}_7\text{H}_9\text{O}_3$   $[\text{M} + \text{H}]^+$ : 141.0552

Found: 141.0552

TLC (50% EtOAc in hexanes),  $R_f$ : 0.15



Methoxylamine hydrochloride (2.26 g, 27.0 mmol, 2.0 equiv) and pyridine (3.30 mL, 40.5 mmol, 3.0 equiv) were added sequentially to an ice-chilled solution of epoxy alcohol **94** (1.92 g, 13.5 mmol, 1 equiv) in methanol (30 mL). The resulting solution was stirred at 23 °C for 5 h. The reaction mixture was poured into water (100 mL), and the product was extracted with ethyl acetate (3 × 80 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash chromatography (20–30% ethyl acetate–hexanes) provided methyloxime **116** (1.95 g) in 84% yield.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 3.96 (br d, 1H,  $J = 12.5$  Hz,  $\text{CH}_2\text{OH}$ ), 3.86 (s, 3H,  $\text{OCH}_3$ ), 3.73 (dd, 1H,  $J = 12.5, 8.0$  Hz,  $\text{CH}_2\text{OH}$ ), 3.43 (d, 1H,  $J = 2.6$  Hz, epoxide H), 2.75 (m, 1H,  $\text{CH}_2\text{OH}$ ), 2.64 (dt, 1H,  $J = 18.4, 4.0$  Hz,  $\text{N}=\text{CCH}_2$ ), 2.13 (dq, 1H,  $J = 14.2, 3.0$  Hz,  $\text{CH}_2$ ), 1.94 (m, 1H,  $\text{CH}_2$ ), 1.42–1.79 (complex, 3H,  $\text{CH}_2$ )

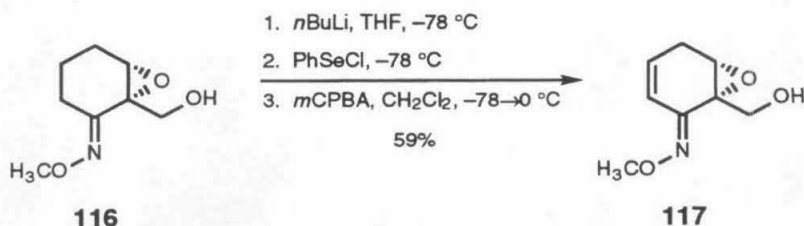
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 155.2 ( $\text{C}=\text{N}$ ), 63.2, 62.2, 58.4, 57.5, 23.4, 22.2, 15.1

FTIR (neat),  $\text{cm}^{-1}$ : 3432 (br, OH), 2940 (m), 1436 (w), 1101 (w), 1049 (s), 902 (w), 763 (w)

HRMS (EI): Calc'd for  $\text{C}_8\text{H}_{12}\text{NO}_3$  [ $\text{M} - \text{H}$ ] $^+$ : 170.0817

Found: 170.0823

TLC (40% EtOAc in hexanes),  $R_f$ : 0.41

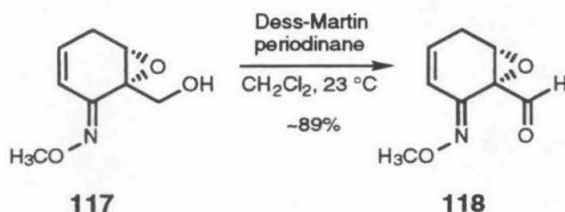


*n*-Butyllithium (3.20 mL of a 2.44 M solution in hexanes, 7.79 mmol, 2.2 equiv) was added dropwise via syringe over 5 min to a degassed, chilled ( $-78\text{ }^{\circ}\text{C}$ ) solution of methyloxime **116** (606 mg, 3.54 mmol, 1 equiv) in tetrahydrofuran (10.0 mL). The reaction mixture was maintained at  $-78\text{ }^{\circ}\text{C}$  for 2.5 h. A solution of phenylselenenyl chloride (817 mg, 4.27 mmol, 1.2 equiv) in THF (3.0 mL) was added to the reaction mixture. After 45 min, the reaction mixture was quenched with addition of water (15 mL), diluted with ethyl acetate (10 mL), and was warmed to  $23\text{ }^{\circ}\text{C}$ . The layers were separated and the aqueous layer was further extracted with ethyl acetate ( $2 \times 10\text{ mL}$ ). The combined organic layers were dried over sodium sulfate and were concentrated.

The resulting crude oil was cooled in a dichloromethane solution (20.0 mL) to  $-78\text{ }^{\circ}\text{C}$ . *m*-Chloroperoxybenzoic acid (1.31 g, 5.31 mmol, 1.5 equiv) was added, and the resulting slurry was stirred at  $-78\text{ }^{\circ}\text{C}$  for 17 min and at  $0\text{ }^{\circ}\text{C}$  for 17 min. The reaction mixture was quenched upon addition of a 1:4 mixture of saturated aqueous sodium carbonate solution and water (40 mL), was diluted with ethyl acetate (40 mL), and was warmed to  $23\text{ }^{\circ}\text{C}$ . The layers were separated, and the aqueous layer was further extracted with ethyl acetate ( $2 \times 20\text{ mL}$ ). The combined organic layers were dried over sodium sulfate and were concentrated. The crude oil was purified by flash chromatography (20–30% ethyl acetate–hexanes) to afford the  $\alpha,\beta$ -unsaturated methyloxime **117** (356 mg, 59%) and the starting material **116** (71.1 mg, 12%). The  $^{13}\text{C}$  NMR spectral assignments were confirmed by an APT experiment.



|   |  |
|---|--|
| $^1\text{H}$ NMR (300 MHz, $\text{CDCl}_3$ ), $\delta$ :    | 6.57 (dt, 1H, $J = 10.4, 2.2$ Hz, $\text{N}=\text{CCH}=\text{CH}$ ),<br>5.92 (dm, 1H, $J = 10.6$ Hz, $\text{N}=\text{CCH}$ ), 4.06 (d,<br>1H, $J = 12.7$ Hz, $\text{CH}_2\text{OH}$ ), 3.91 (s, 3H, $\text{OCH}_3$ ),<br>3.84 (br d, 1H, $J = 12.7$ Hz, $\text{CH}_2\text{OH}$ ), 3.56 (m,<br>1H, epoxide <b>H</b> ), 2.81 (ddt, 1H, $J = 21.0, 4.9,$<br>1.4 Hz, $\text{CH}_2$ ), 2.70 (br, 1H, $\text{CH}_2\text{OH}$ ), 2.60 (dq,<br>1H, $J = 21.0, 2.8$ Hz, $\text{CH}_2$ ) |
| $^{13}\text{C}$ NMR (100 MHz, $\text{CDCl}_3$ ), $\delta$ : | 149.9 ( $\text{C}=\text{N}$ ), 132.5 ( $\text{N}=\text{CCH}=\text{CH}$ ), 115.0<br>( $\text{N}=\text{CCH}$ ), 62.4 ( $\text{OCH}_3$ ), 62.3 ( $\text{CH}_2\text{OH}$ ), 58.2<br>(epoxide <b>C</b> ), 55.5 (epoxide <b>CH</b> ), 27.0 ( $\text{CH}_2$ )   |
| FTIR (neat), $\text{cm}^{-1}$ :                             | 3419 (br, OH), 2939 (w), 1634 (w, $\text{C}=\text{N}$ ), 1411<br>(w), 1052 (s), 903 (m), 746 (w)   |
| HRMS (EI):  | Calc'd for $\text{C}_8\text{H}_{10}\text{NO}_3$ $[\text{M} - \text{H}]^+$ : 168.0661<br>Found: 168.0664  |
| TLC (50% EtOAc in hexanes), $R_f$ :                         | 0.39   |

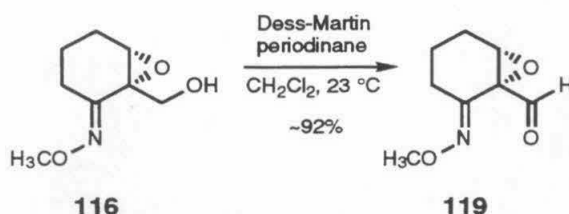


The Dess–Martin periodinane (380 mg, 895  $\mu\text{mol}$ , 1.5 equiv) was added to an ice-cooled solution of alcohol **117** (101 mg, 597  $\mu\text{mol}$ , 1 equiv) in dichloromethane (3.0 mL). The resulting slurry was stirred vigorously at 23  $^\circ\text{C}$  for 25 min. The reaction mixture was diluted with diethyl ether (6 mL) and a 1:1 mixture of saturated aqueous sodium bicarbonate solution and saturated aqueous sodium thiosulfate solution (6 mL) and was stirred at 23  $^\circ\text{C}$ . After 35 min, the layers were separated, and the aqueous layer was further extracted with diethyl ether ( $2 \times 6$  mL). The combined organic layers were dried over sodium sulfate and were concentrated to give the crude aldehyde **118** (88.5 mg, ~89%) as a yellow solid.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 10.07 (s, 1H, CHO), 6.66 (dt, 1H,  $J = 10.6, 2.2$  Hz,  $\text{N}=\text{CCH}=\text{CH}$ ), 5.95 (dm, 1H,  $J = 10.6$  Hz,  $\text{N}=\text{CCH}$ ), 3.98 (s, 3H,  $\text{OCH}_3$ ), 3.62 (br, 1H, epoxide H), 2.86 (dd, 1H,  $J = 21.1, 4.4$  Hz,  $\text{CH}_2$ ), 2.69 (dq, 1H,  $J = 21.0, 2.9$  Hz,  $\text{CH}_2$ )

FTIR (neat),  $\text{cm}^{-1}$ : 3424 (br), 2940 (w), 1729 (C=O), 1630 (w), 1412 (w), 1051 (s), 909 (m), 830 (m)

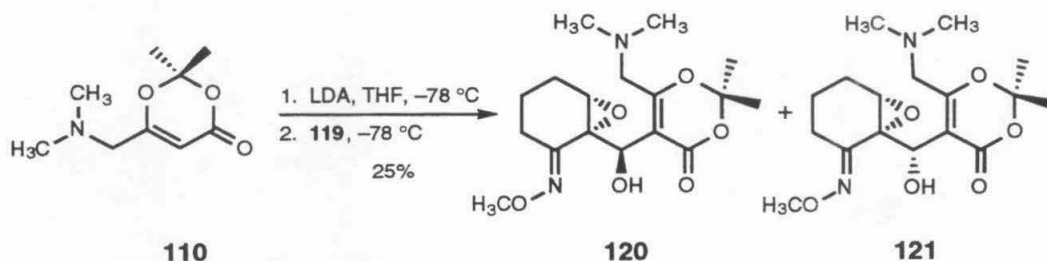
TLC (60% EtOAc in hexanes),  $R_f$ : 0.43–0.66



The Dess–Martin periodinane (368 mg, 868  $\mu\text{mol}$ , 1.5 equiv) was added to an ice-cooled solution of alcohol **116** (99.1 mg, 579  $\mu\text{mol}$ , 1 equiv) in dichloromethane (3.0 mL). The resulting slurry was stirred vigorously at 23  $^\circ\text{C}$  for 20 min. The reaction mixture was diluted with diethyl ether (5 mL) and a 1:1 mixture of saturated aqueous sodium bicarbonate solution and saturated aqueous sodium thiosulfate solution (5 mL) and was stirred at 23  $^\circ\text{C}$ . After 30 min, the layers were separated, and the aqueous layer was further extracted with diethyl ether (2  $\times$  5 mL). The combined organic layers were dried over sodium sulfate and were concentrated to give the crude aldehyde **119** (89.9 mg, ~92%) as a yellow solid.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 9.94 (s, 1H, CHO), 3.93 (s, 3H,  $\text{OCH}_3$ ), 3.54 (d, 1H,  $J = 2.6$  Hz, epoxide H), 2.83 (dt, 1H,  $J = 17.9, 3.1$  Hz,  $\text{CH}_2$ ), 2.23 (dq, 1H,  $J = 15.2, 3.2$  Hz,  $\text{CH}_2$ ), 1.52–1.96 (complex, 4H,  $\text{CH}_2$ )

TLC (50% EtOAc in hexanes),  $R_f$ : 0.32–0.62



*n*-Butyllithium (285  $\mu\text{L}$  of a 1.25 M solution in hexanes, 358  $\mu\text{mol}$ , 2.20 equiv) was added to a degassed, chilled ( $-78\text{ }^{\circ}\text{C}$ ) solution of diisopropylamine (51  $\mu\text{L}$ , 366  $\mu\text{mol}$ , 2.25 equiv) in tetrahydrofuran (1.0 mL). The solution was warmed to  $0\text{ }^{\circ}\text{C}$  for 10 min and was then cooled to  $-78\text{ }^{\circ}\text{C}$ . A solution of amine **110** (64.1 mg, 346  $\mu\text{mol}$ , 2.1 equiv) in THF (500  $\mu\text{L}$ ) was added to the reaction mixture. The resulting solution was maintained at  $-78\text{ }^{\circ}\text{C}$  for 35 min and was then added to the crude aldehyde **119** (27.5 mg, 163  $\mu\text{mol}$ , 1 equiv) at  $-78\text{ }^{\circ}\text{C}$ . After 25 min, water (5 mL) was added to the reaction mixture, and the solution was warmed to  $23\text{ }^{\circ}\text{C}$ . The product was extracted with ethyl acetate ( $3 \times 5\text{ mL}$ ). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash chromatography (50–100% ethyl acetate–hexanes) provided the aldol adduct **120** (10.1 mg, 18%) and its diastereomer **121** (3.9 mg, 7%) in addition to aldehyde **119** (12.9 mg, 47%). The diastereomers were arbitrarily assigned. The  $^{13}\text{C}$  NMR spectral assignments were confirmed by an APT experiment.

#### Aldol adduct **120**:

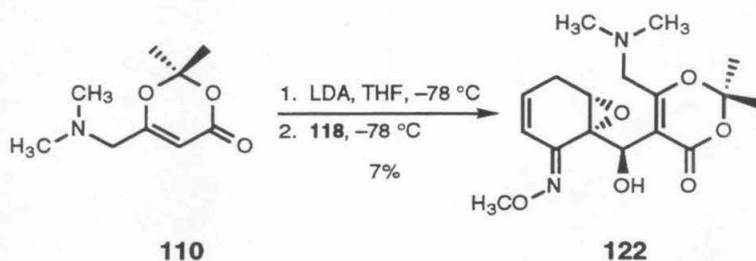
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 7.86 (br, 1H, OH), 5.35 (s, 1H, CHOH), 4.30 (d, 1H,  $J = 13.7\text{ Hz}$ ,  $\text{CH}_2\text{N}(\text{CH}_3)_2$ ), 3.93 (br, 1H, epoxide H), 3.82 (s, 3H,  $\text{OCH}_3$ ), 2.56 (dt, 1H,  $J = 18.1, 4.2\text{ Hz}$ ,  $\text{CH}_2$ ), 2.52 (d, 1H,  $J = 13.9\text{ Hz}$ ,  $\text{CH}_2\text{N}(\text{CH}_3)_2$ ), 2.28 (s, 6H,  $\text{N}(\text{CH}_3)_2$ ), 1.96–2.17 (complex, 2H,  $\text{CH}_2$ ), 1.46–1.82 (complex, 3H,  $\text{CH}_2$ ), 1.70 (s, 3H,  $\text{CH}_3$ ), 1.68 (s,

|   |  |
|---|--|
|   | 3H, CH <sub>3</sub> )  |
| <sup>13</sup> C NMR (100 MHz, CDCl <sub>3</sub> ), δ: | 163.8 (C(O)C=C), 162.1 (C=O), 154.3 (C=N),<br>111.8 (C(O)C), 104.8 (C(CH <sub>3</sub> ) <sub>2</sub> ), 63.4 (OCH <sub>3</sub> ,<br>epoxide C), 61.9 (epoxide CH), 60.6<br>(CH <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub> ), 55.6 (CHOH), 44.6 (N(CH <sub>3</sub> ) <sub>2</sub> ),<br>27.3 (CH <sub>3</sub> ), 24.1 (CH <sub>3</sub> ), 23.3 (CH <sub>2</sub> ), 22.4<br>(CH <sub>2</sub> ), 15.5 (CH <sub>2</sub> )   |
| FTIR (neat), cm <sup>-1</sup> :                       | 3434 (br, OH), 2943 (m), 1729 (s, C=O), 1627<br>(m), 1395 (m), 1275 (m), 1206 (m), 1045 (s)  |
| HRMS (CI):  | Calc'd for C <sub>17</sub> H <sub>27</sub> N <sub>2</sub> O <sub>6</sub> [M + H] <sup>+</sup> : 355.1869<br>Found: 355.1873  |
| TLC (EtOAc), R <sub>f</sub> :                         | 0.37   |
| Aldol adduct <b>121</b> :                             |  |
| <sup>1</sup> H NMR (300 MHz, CDCl <sub>3</sub> ), δ:  | 5.33 (s, 1H, CHOH), 3.79 (s, 3H, OCH <sub>3</sub> ), 3.76<br>(br, 1H, epoxide H), 3.33 (ABq, 2H, J = 14.0<br>Hz, Δν = 150.5 Hz, CH <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub> ), 2.80 (dt, 1H,<br>J = 17.4, 3.4 Hz, CH <sub>2</sub> ), 2.35 (s, 6H, N(CH <sub>3</sub> ) <sub>2</sub> ),<br>2.16 (dq, 1H, J = 15.0, 3.4 Hz, CH <sub>2</sub> ), 1.49–2.00<br>(complex, 4H, CH <sub>2</sub> ), 1.69 (s, 3H, CH <sub>3</sub> ), 1.66 (s,<br>3H, CH <sub>3</sub> ) |
| <sup>13</sup> C NMR (100 MHz, CDCl <sub>3</sub> ), δ: | 167.2 (C(O)C=C), 160.6 (C=O), 155.2 (C=N),<br>108.0 (C(O)C), 105.5 (C(CH <sub>3</sub> ) <sub>2</sub> ), 64.1 (OCH <sub>3</sub> ),<br>61.7 (epoxide CH), 59.6 (epoxide C), 59.2<br>(CH <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub> ), 57.1 (CHOH), 45.5 (N(CH <sub>3</sub> ) <sub>2</sub> ),<br>26.6 (CH <sub>3</sub> ), 23.4 (CH <sub>3</sub> ), 23.0 (CH <sub>2</sub> ), 21.9<br>(CH <sub>2</sub> ), 15.4 (CH <sub>2</sub> )                                  |

FTIR (neat),  $\text{cm}^{-1}$ : 3415 (br, OH), 2942 (m), 1728 (s, C=O), 1627 (m), 1391 (m), 1271 (m), 1206 (m), 1046 (s)

HRMS (FAB): Calc'd for  $\text{C}_{17}\text{H}_{27}\text{N}_2\text{O}_6$   $[\text{M} + \text{H}]^+$ : 355.1869  
Found: 355.1880

TLC (EtOAc),  $R_f$ : 0.15

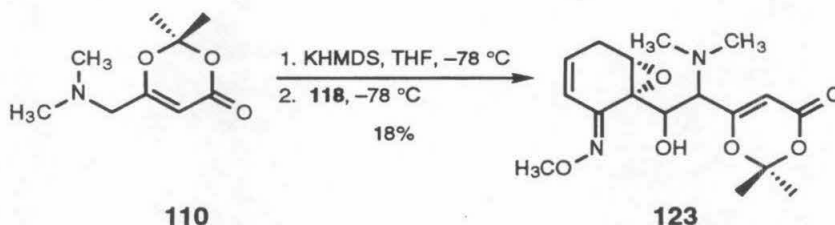


*n*-Butyllithium (215  $\mu$ L of a 2.35 M solution in hexanes, 505  $\mu$ mol, 2.2 equiv) was added to a degassed, chilled ( $-78\text{ }^{\circ}\text{C}$ ) solution of diisopropylamine (74  $\mu$ L, 528  $\mu$ mol, 2.3 equiv) in tetrahydrofuran (1.5 mL). The solution was warmed to  $0\text{ }^{\circ}\text{C}$  for 10 min and was then cooled to  $-78\text{ }^{\circ}\text{C}$ . A solution of amine **110** (90.1 mg, 486  $\mu$ mol, 2.1 equiv) in THF (1.0 mL) was added to the reaction mixture. The resulting solution was maintained at  $-78\text{ }^{\circ}\text{C}$  for 35 min, at which point a solution of the crude aldehyde **118** (38.4 mg, 230  $\mu$ mol, 1 equiv) in tetrahydrofuran (500  $\mu$ L) was added. After 30 min, water (5 mL) was added to the reaction mixture, and the solution was warmed to  $23\text{ }^{\circ}\text{C}$ . The product was extracted with ethyl acetate ( $3 \times 5$  mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash chromatography (60% ethyl acetate–hexanes) provided the aldol adduct **122** (5.5 mg, 7%), based on its similarity to aldol adduct **120**. The diastereomer of **122** was visible by TLC ( $R_f = 0.10$  in ethyl acetate) but was not isolable.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 6.56 (dt, 1H,  $J = 10.6, 1.9\text{ Hz}$ ,  $\text{N}=\text{CCH}=\text{CH}$ ), 5.92 (dm, 1H,  $J = 10.5\text{ Hz}$ ,  $\text{N}=\text{CCH}$ ), 5.44 (s, 1H,  $\text{CHOH}$ ), 4.35 (d, 1H,  $J = 13.9\text{ Hz}$ ,  $\text{CH}_2\text{N}(\text{CH}_3)_2$ ), 4.08 (br, 1H, epoxide **H**), 3.87 (s, 3H,  $\text{OCH}_3$ ), 2.81 (m, 1H,  $\text{CH}_2$ ), 2.64 (dq, 1H,  $J = 21.0, 2.7\text{ Hz}$ ,  $\text{CH}_2$ ), 2.50 (d, 1H,  $J = 13.9\text{ Hz}$ ,  $\text{CH}_2\text{N}(\text{CH}_3)_2$ ), 2.29 (s, 6H,  $\text{N}(\text{CH}_3)_2$ ), 1.70 (s, 3H,  $\text{CH}_3$ ), 1.69 (s, 3H,  $\text{CH}_3$ )

|   |   |
|---|---|
| $^{13}\text{C}$ NMR (100 MHz, $\text{CDCl}_3$ ), $\delta$ : | 163.9 (C(O)C=C), 161.9 (C=O), 149.5 (C=N),<br>131.8 (N=CCH=CH), 115.5 (N=CCH), 111.8<br>(C(O)C), 104.8 (C(CH <sub>3</sub> ) <sub>2</sub> ), 63.9, 62.8, 62.2,<br>60.8, 54.0, 44.5 (N(CH <sub>3</sub> ) <sub>2</sub> ), 27.4, 27.1, 24.0 |
| FTIR (neat), $\text{cm}^{-1}$ :                             | 3418 (br, OH), 2940 (w), 1728 (s, C=O), 1627<br>(m), 1395 (m), 1274 (m), 1207 (m), 1047 (s)   |
| HRMS (CI):  | Calc'd for $\text{C}_{17}\text{H}_{25}\text{N}_2\text{O}_6$ $[\text{M} + \text{H}]^+$ : 353.1712<br>Found: 353.1709   |
| TLC (EtOAc), $R_f$ :  | 0.34  |



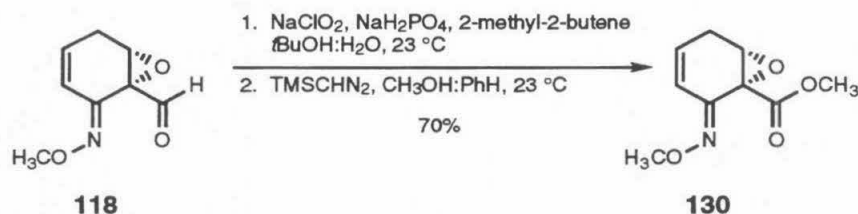


Potassium bis(trimethylsilyl)amide (360  $\mu\text{L}$  of a 0.5 M solution in toluene, 181  $\mu\text{mol}$ , 1.7 equiv) was added to a degassed, chilled ( $-78\text{ }^\circ\text{C}$ ) solution of amine **110** (29.2 mg, 158  $\mu\text{mol}$ , 1.5 equiv) in tetrahydrofuran (1.0 mL). After 1 h, a solution of crude aldehyde **118** (17.8 mg, 106  $\mu\text{mol}$ , 1 equiv) in THF (500  $\mu\text{L}$ ) was added to the reaction mixture. After 20 min, the reaction mixture was quenched upon addition of water (5 mL), and the product was extracted with dichloromethane ( $3 \times 5\text{ mL}$ ). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash chromatography (60–70% ethyl acetate–hexanes) to provide the aldol adduct **123** (6.8 mg, 18%). The  $^{13}\text{C}$  NMR spectral assignments were confirmed by an APT experiment.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 6.61 (dt, 1H,  $J = 10.6, 2.0\text{ Hz}$ ,  $\text{N}=\text{CCH}=\text{CH}$ ), 5.93 (dm, 1H,  $J = 10.5\text{ Hz}$ ,  $\text{N}=\text{CCH}$ ), 5.28 (s, 1H,  $\text{C}(\text{O})\text{CH}$ ), 4.89 (d, 1H,  $J = 5.6\text{ Hz}$ ,  $\text{CHN}(\text{CH}_3)_2$ ), 3.95 (s, 3H,  $\text{OCH}_3$ ), 3.77 (br, 1H, epoxide H), 3.22 (d, 1H,  $J = 5.6\text{ Hz}$ ,  $\text{CHOH}$ ), 2.80 (dd, 1H,  $J = 21.8, 4.6\text{ Hz}$ ,  $\text{CH}_2$ ), 2.64 (br, 1H, OH), 2.54 (dq, 1H,  $J = 21.4, 2.8\text{ Hz}$ ,  $\text{CH}_2$ ), 2.36 (s, 6H,  $\text{N}(\text{CH}_3)_2$ ), 1.73 (s, 3H,  $\text{CH}_3$ ), 1.70 (s, 3H,  $\text{CH}_3$ )

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 167.9, 160.7, 132.0 ( $\text{N}=\text{CCH}=\text{CH}$ ), 114.7 ( $\text{N}=\text{CCH}$ ), 110.0, 107.0, 96.3 ( $\text{C}(\text{O})\text{CH}$ ), 69.1

(CHN(CH<sub>3</sub>)<sub>2</sub>), 65.2 (OCH<sub>3</sub>), 62.5 (epoxide CH),  
58.6 (epoxide C), 53.8 (CHOH), 43.2  
(N(CH<sub>3</sub>)<sub>2</sub>), 26.6 (CH<sub>2</sub>), 25.6 (CH<sub>3</sub>), 24.7 (CH<sub>3</sub>)  
FTIR (neat), cm<sup>-1</sup>: 3482 (br, OH), 2940 (w), 1729 (C=O), 1625 (m),  
1392 (m), 1272 (m), 1203 (m), 1050 (s)  
HRMS (CI): Calc'd for C<sub>17</sub>H<sub>25</sub>N<sub>2</sub>O<sub>6</sub> [M + H]<sup>+</sup>: 353.1712  
Found: 353.1706  
TLC (EtOAc), R<sub>f</sub>: 0.42



Sodium chlorite (414 mg of technical grade (80%) reagent, 3.66 mmol, 4.0 equiv) was added to a solution of crude aldehyde **118** (153 mg, 915  $\mu\text{mol}$ , 1 equiv), 2-methyl-2-butene (2.30 mL of a 2.0 M solution in THF, 4.58 mmol, 5.0 equiv), and sodium dihydrogenphosphate (1.26 mL of a 1.45 M aqueous solution, 1.83 mmol, 2.0 equiv) in *tert*-butyl alcohol (4.5 mL; 0.20 M **118** in *t*-BuOH). The biphasic reaction mixture was stirred vigorously at 23  $^\circ\text{C}$  for 40 min. A 1:4 mixture of 1 N aqueous HCl solution and 0.9 M aqueous potassium dihydrogenphosphate solution (10 mL) and brine (2 mL) were added to the reaction mixture. The product was extracted with dichloromethane ( $3 \times 10$  mL). The combined organic layers were dried over sodium sulfate and were concentrated. The crude oil was diluted with benzene (4.0 mL) and methanol (1.0 mL) at 23  $^\circ\text{C}$ . (Trimethylsilyl)diazomethane (825  $\mu\text{L}$  of a 2.0 M solution in hexanes, 1.65 mmol, 1.8 equiv) was added to the reaction mixture. After 20 min, the reaction mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography (20% ethyl acetate–hexanes) afforded methyl ester **130** (126 mg, 70%) as a pale yellow oil.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 6.62 (dt, 1H,  $J = 10.8, 2.2$  Hz,  $\text{N}=\text{CCH}=\text{CH}$ ), 5.91 (dm, 1H,  $J = 10.9$  Hz,  $\text{N}=\text{CCH}$ ), 3.93 (s, 3H,  $\text{NOCH}_3$ ), 3.82 (s, 3H,  $\text{OCH}_3$ ), 3.64 (m, 1H, epoxide H), 2.83 (dm, 1H,  $J = 21.6$  Hz,  $\text{CH}_2$ ), 2.69 (dq, 1H,  $J = 21.2, 2.9$  Hz,  $\text{CH}_2$ )

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 167.3 (C=O), 146.2 (C=N), 131.1

(N=CCH=CH), 114.5 (N=CCH), 94.7 (epoxide C), 62.6, 57.4 (epoxide CH), 56.5, 52.5, 26.4 (CH<sub>2</sub>)

FTIR (neat), cm<sup>-1</sup>:

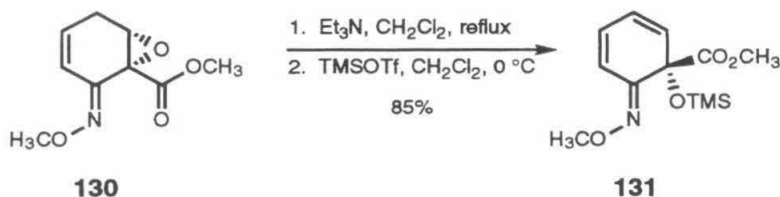
2943 (w), 1749 (s, C=O), 1631 (w), 1441 (m), 1290 (m), 1248 (s), 1051 (s), 907 (m)

HRMS (CI):

Calc'd for C<sub>9</sub>H<sub>12</sub>NO<sub>4</sub> [M - H]<sup>+</sup>: 198.0766

Found: 198.0768

TLC (60% EtOAc in hexanes), *R<sub>f</sub>*: 0.57



Triethylamine (270  $\mu\text{L}$ , 1.93 mmol, 10.0 equiv) was added to a solution of methyl ester **130** (38.1 mg, 193  $\mu\text{mol}$ , 1 equiv) in dichloromethane (2.0 mL). The reaction mixture was heated to reflux for 6 h. The reaction mixture containing the intermediate diene was then cooled to 0  $^{\circ}\text{C}$ . Trimethylsilyl trifluoromethanesulfonate (75  $\mu\text{L}$ , 386  $\mu\text{mol}$ , 2.0 equiv) was added dropwise by syringe. After 20 min, the reaction mixture was quenched upon the addition of water (5 mL) and brine (2 mL), diluted with ethyl acetate (5 mL), and was warmed to 23  $^{\circ}\text{C}$ . The layers were separated, and the aqueous layer was further extracted with ethyl acetate (2  $\times$  5 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash chromatography (10% ethyl acetate–hexanes) provided the trimethylsilyl ether **131** (44.4 mg, 85%) as a white solid.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 6.75 (d, 1H,  $J = 10.0$  Hz,  $\text{CH}=\text{CH}$ ), 6.16–6.30 (complex, 2H,  $\text{CH}=\text{CHCH}=\text{CH}$ ), 5.96 (d, 1H,  $J = 9.5$  Hz,  $\text{N}=\text{CCH}$ ), 3.97 (s, 3H,  $\text{NOCH}_3$ ), 3.74 (s, 3H,  $\text{OCH}_3$ ), 0.13 (s, 9H,  $\text{Si}(\text{CH}_3)_3$ )

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 171.5 ( $\text{C}=\text{O}$ ), 153.7 ( $\text{C}=\text{N}$ ), 131.9, 127.9, 123.7, 113.8, 74.3 ( $\text{COTMS}$ ), 62.6 ( $\text{NOCH}_3$ ), 52.8 ( $\text{OCH}_3$ ), 1.9 ( $\text{Si}(\text{CH}_3)_3$ )

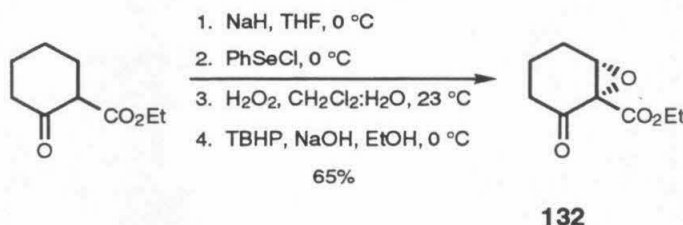
FTIR (neat),  $\text{cm}^{-1}$ : 2956 (w), 1756 (s,  $\text{C}=\text{O}$ ), 1411 (w), 1250 (m), 1132 (s), 1051 (s), 842 (s)

HRMS (CI): Calc'd for  $\text{C}_9\text{H}_{19}\text{NO}_4\text{Si}$   $[\text{M}]^+$ : 269.1083  
Found: 269.1077

TLC (3:1:1 EtOAc:toluene:hexane),

$R_f$ :

0.58



2-Carbethoxy-2-cyclohexen-1-one was prepared from 2-carbethoxycyclohexanone (1.06 g, 6.25 mmol, 1 equiv) by the procedure of Reich and co-workers.<sup>86</sup> The crude product (th. yield = 6.25 mmol) was diluted with ethanol (10.0 mL) and was cooled to 0 °C. *tert*-Butyl hydroperoxide (2.50 mL of a 70% aqueous solution, 18.8 mmol, 3.0 equiv) and sodium hydroxide (105  $\mu$ L of a 6 N aqueous solution, 625  $\mu$ mol, 0.1 equiv) were added sequentially to the reaction mixture. After 30 min, the reaction mixture was poured into water (30 mL) and brine (10 mL), and the product was extracted with ethyl acetate (3  $\times$  30 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash chromatography (20% ethyl acetate–hexanes) afforded epoxide **132** (743 mg) in 65% yield from commercially available starting material.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>),  $\delta$ : 4.27 (q, 2H,  $J$  = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 3.66 (m, 1H, epoxide H), 2.55 (dt, 1H,  $J$  = 17.2, 4.2 Hz, C(O)CH<sub>2</sub>), 2.32 (m, 1H, C(O)CH<sub>2</sub>), 1.71–2.21 (complex, 4H, CH<sub>2</sub>), 1.29 (t, 3H,  $J$  = 7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>)

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>),  $\delta$ : 199.1 (C=O), 165.5 (CO<sub>2</sub>Et), 61.3, 59.4, 58.1, 36.8, 22.2, 15.9, 13.5

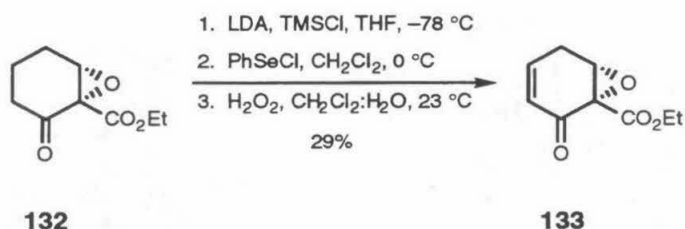
FTIR (neat), cm<sup>-1</sup>: 2956 (w), 1748 (s, C=O), 1717 (s, C=O), 1282 (m), 1224 (m), 1060 (m)

HRMS (CI): Calc'd for C<sub>9</sub>H<sub>13</sub>O<sub>4</sub> [M + H]<sup>+</sup>: 185.0814

Found: 185.0817

TLC (40% EtOAc in hexanes),  $R_f$ : 0.45





*n*-Butyllithium (525  $\mu\text{L}$  of a 2.35 M solution in hexanes, 1.24 mmol, 1.20 equiv) was added to a degassed, cooled ( $-78\text{ }^{\circ}\text{C}$ ) solution of diisopropylamine (180  $\mu\text{L}$ , 1.29 mmol, 1.25 equiv) in tetrahydrofuran (4.0 mL). The resulting solution was stirred at  $0\text{ }^{\circ}\text{C}$  for 10 min and was then cooled to  $-78\text{ }^{\circ}\text{C}$ . Chlorotrimethylsilane (325  $\mu\text{L}$ , 2.58 mmol, 2.5 equiv) was added to the reaction mixture, followed 5 min later by the dropwise addition of ketone **132** (190 mg, 1.03 mmol, 1 equiv) in THF (1.0 mL). After 20 min, the reaction mixture was quenched upon addition of triethylamine (430  $\mu\text{L}$ , 3.09 mmol, 3.0 equiv), and the resulting solution was poured into saturated aqueous sodium bicarbonate solution (10 mL). The product was extracted with a 1:1 mixture of ethyl acetate and hexanes ( $3 \times 10\text{ mL}$ ). The combined organic layers were dried over sodium sulfate and were concentrated.

The crude oil was diluted with dichloromethane (4.0 mL) and was cooled to  $0\text{ }^{\circ}\text{C}$ . A solution of phenylselenenyl chloride (237 mg, 1.24 mmol, 1.2 equiv) in dichloromethane (1.0 mL) was added, and the resulting reaction mixture was stirred at  $0\text{ }^{\circ}\text{C}$ . After 30 min, a 1:4 mixture of saturated aqueous sodium carbonate solution and water (10 mL) was added to the reaction mixture. The product was extracted with a 1:1 mixture of ethyl acetate and hexanes ( $3 \times 8\text{ mL}$ ). The combined organic layers were dried over sodium sulfate and were concentrated.

This crude oil was diluted with dichloromethane (4.0 mL) and water (1.0 mL) and was cooled to  $0\text{ }^{\circ}\text{C}$ . Hydrogen peroxide (257 mg of a 30% (w/w) aqueous solution, 2.27 mmol, 2.2 equiv) was added, and the reaction mixture was stirred vigorously at  $23\text{ }^{\circ}\text{C}$ . After 20 min, the reaction mixture was diluted with water (10 mL) and the product was extracted with ethyl acetate ( $3 \times 10\text{ mL}$ ). The combined organic layers were dried over

sodium sulfate and were concentrated. Rapid purification of the residue by flash chromatography (35% ethyl acetate–hexanes) provided enone **133** (53.7 mg, 29%).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 6.58 (dm, 1H,  $J = 10.6$  Hz,  $\text{C}(\text{O})\text{CH}=\text{CH}$ ), 6.02 (dt, 1H,  $J = 10.5, 2.2$  Hz,  $\text{C}(\text{O})\text{CH}$ ), 4.26 (q, 2H,  $J = 7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 3.80 (m, 1H, epoxide H), 2.97 (ddm, 1H,  $J = 22.3, 4.8$  Hz,  $\text{CH}_2$ ), 2.81 (dq, 1H,  $J = 21.6, 2.8$  Hz,  $\text{CH}_2$ ), 1.28 (t, 3H,  $J = 7.2$  Hz,  $\text{OCH}_2\text{CH}_3$ )

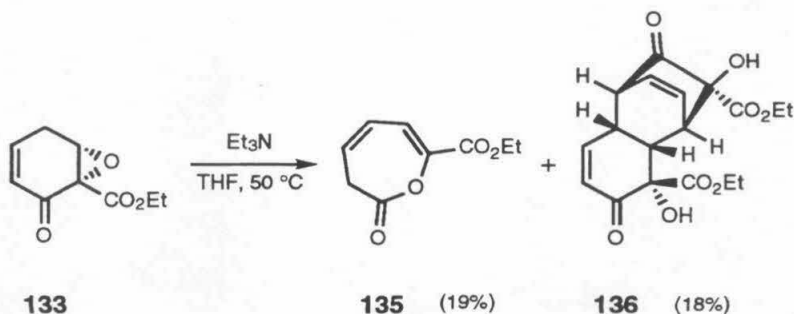
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 188.7 ( $\text{C}=\text{O}$ ), 165.4 ( $\text{CO}_2\text{Et}$ ), 143.3 ( $\text{C}(\text{O})\text{CH}=\text{CH}$ ), 126.4 ( $\text{C}(\text{O})\text{CH}$ ), 62.0, 58.1, 57.7, 26.5, 13.9

FTIR (neat),  $\text{cm}^{-1}$ : 2986 (w), 1748 (s,  $\text{C}=\text{O}$ ), 1680 (s,  $\text{C}=\text{O}$ ), 1399 (m), 1291 (m), 1240 (m), 1063 (s), 824 (m)

HRMS (EI): Calc'd for  $\text{C}_9\text{H}_{10}\text{O}_4$   $[\text{M}]^+$ : 182.0579

Found: 182.0580

TLC (30% EtOAc in hexanes),  $R_f$ : 0.15



Triethylamine (60  $\mu\text{L}$ , 430  $\mu\text{mol}$ , 10.0 equiv) was added to a solution of enone **133** (7.9 mg, 43  $\mu\text{mol}$ , 1 equiv) in tetrahydrofuran (1.0 mL; 0.043 M **133** in THF) at 23  $^{\circ}\text{C}$ . The reaction mixture was warmed at 50  $^{\circ}\text{C}$  for 30 min and was then cooled to 23  $^{\circ}\text{C}$ . The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography (25% ethyl acetate–hexanes; 50% ethyl acetate–hexanes) to provide lactone **135** (1.5 mg, 19%) as a colorless oil and dimer **136** (2.8 mg, 18%) as a yellow solid.

#### Lactone **135**:

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 7.17 (d, 1H,  $J = 5.4$  Hz,  $\text{CH}=\text{CCO}_2\text{Et}$ ), 6.39 (dd, 1H,  $J = 9.4, 5.7$  Hz,  $\text{CH}=\text{CHCH}=\text{C}$ ), 6.07 (dt, 1H,  $J = 9.5, 6.4$  Hz,  $\text{CH}_2\text{CH}$ ), 4.33 (q, 2H,  $J = 7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 3.12 (d, 2H,  $J = 6.7$  Hz,  $\text{CH}_2$ ), 1.36 (t, 3H,  $J = 7.2$  Hz,  $\text{OCH}_2\text{CH}_3$ )

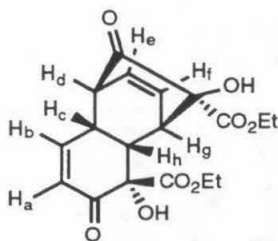
$^{13}\text{C}$  NMR (100 MHz, acetone- $d_6$ )  $\delta$ : 166.1 ( $\text{C}=\text{O}$ ), 161.9 ( $\text{C}=\text{O}$ ), 141.6 ( $\text{CCO}_2\text{Et}$ ), 128.4, 127.3, 120.0, 62.3, 36.7, 14.4

FTIR (neat),  $\text{cm}^{-1}$ : 2984 (w), 1777 (s,  $\text{C}=\text{O}$ ), 1729 (s,  $\text{C}=\text{O}$ ), 1597 (w), 1277 (s), 1122 (s)

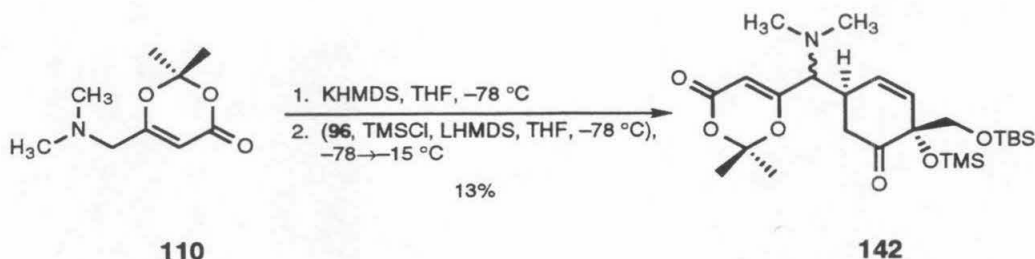
HRMS (CI): Calc'd for  $\text{C}_9\text{H}_{10}\text{O}_4$   $[\text{M}]^+$ : 182.0579

Found: 182.0577

TLC (60% EtOAc in hexanes),  $R_f$ : 0.69

**136****Dimer 136:**

|   |   |
|---|---|
| <sup>1</sup> H NMR (300 MHz, CDCl <sub>3</sub> ), δ:  | 6.61 (dd, 1H, <i>J</i> = 10.2, 4.4 Hz, <b>H<sub>b</sub></b> ), 6.34 (td, 1H, <i>J</i> = 7.3, 1.0 Hz, <b>H<sub>f</sub></b> ), 6.16 (dd, 1H, <i>J</i> = 10.0, 1.7 Hz, <b>H<sub>a</sub></b> ), 5.92 (td, 1H, <i>J</i> = 7.3, 1.3 Hz, <b>H<sub>e</sub></b> ), 4.51 (s, 1H, OH), 4.15 (m, 4H, OCH <sub>2</sub> CH <sub>3</sub> ), 3.87 (dd, 1H, <i>J</i> = 8.2, 2.0 Hz, <b>H<sub>h</sub></b> ), 3.79 (s, 1H, OH), 3.58 (m, 2H, <b>H<sub>c</sub></b> , <b>H<sub>g</sub></b> ), 3.36 (m, 1H, <b>H<sub>d</sub></b> ), 1.22 (m, 6H, OCH <sub>2</sub> CH <sub>3</sub> ) |
| <sup>13</sup> C NMR (100 MHz, CD <sub>3</sub> CN), δ: | 205.4, 195.0, 171.1, 170.3, 149.6, 134.4, 130.0, 128.5, 79.7, 77.8, 63.3, 62.9, 52.4, 42.9, 41.5, 37.7, 14.2, 14.1  |
| FTIR (neat), cm <sup>-1</sup> :                       | 3444 (br, OH), 2924 (w), 1734 (s, C=O), 1696 (s, C=O), 1254 (m), 1214 (m), 1125 (m), 1020 (s)   |
| HRMS (CI):  | Calc'd for C <sub>18</sub> H <sub>24</sub> NO <sub>8</sub> [M + NH <sub>4</sub> ] <sup>+</sup> : 382.1502<br>Found: 382.1507  |
| TLC (60% EtOAc in hexanes), <i>R<sub>f</sub></i> :    | 0.50  |

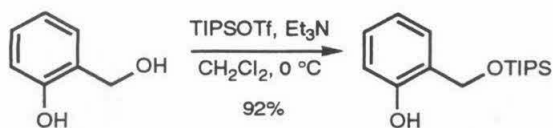


Potassium bis(trimethylsilyl)amide (480  $\mu\text{L}$  of a 0.5 M solution in toluene, 241  $\mu\text{mol}$ , 3.0 equiv) was added to a degassed, cooled ( $-78\text{ }^{\circ}\text{C}$ ) solution of amine **110** (41.6 mg, 225  $\mu\text{mol}$ , 2.8 equiv) in tetrahydrofuran (0.5 mL). The resulting solution was maintained at  $-78\text{ }^{\circ}\text{C}$  for 75 min. Lithium bis(trimethylsilyl)amide (96  $\mu\text{L}$  of a 1.0 M solution in THF, 96  $\mu\text{mol}$ , 1.2 equiv) was added to a degassed, cooled ( $-78\text{ }^{\circ}\text{C}$ ) solution of enone **96** (20.4 mg, 80.2  $\mu\text{mol}$ , 1 equiv) and chlorotrimethylsilane (13  $\mu\text{L}$ , 104  $\mu\text{mol}$ , 1.3 equiv) in tetrahydrofuran (2.0 mL; 0.040 M **96** in THF). The reaction mixture containing the amine substrate was then immediately transferred to the reaction mixture containing the enone substrate. The resulting reaction mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 25 min and was then warmed to  $-40\text{ }^{\circ}\text{C}$ . Over the next 60 min, the reaction mixture was allowed to warm slowly to  $-15\text{ }^{\circ}\text{C}$ . The reaction mixture was quenched upon the addition of water (5 mL), and the products were extracted with ethyl acetate ( $3 \times 5\text{ mL}$ ). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash chromatography (10–15% ethyl acetate–hexanes) afforded adduct **142** (5.3 mg, 13%) as an inseparable mixture of diastereomers (2.5:1), in addition to 2-*t*-butyldimethylsilyloxy phenol **138** (5.5 mg, 30%) and 2,3-dihydroxybenzyl TBS-ether **139** (1.7 mg, 8%).

Adduct **142** (major diastereomer):

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 6.28 (d, 1H,  $J = 9.8\text{ Hz}$ ,  $\text{CHCOTMS}$ ), 5.67 (dd, 1H,  $J = 10.2, 2.3\text{ Hz}$ ,  $\text{CH}=\text{CHCOTMS}$ ), 5.18 (s, 1H,  $\text{C(O)CH}$ ), 3.56 (ABq, 2H,  $J = 9.4\text{ Hz}$ ,  $\Delta\nu =$

|   |  |
|---|--|
|   | 35.5 Hz, $\text{CH}_2\text{OTBS}$ ), 2.96 (m, 1H, $\text{CH}$ ), 2.79 (m, 1H, $\text{CH}$ ), 2.51 (m, 2H, $\text{CH}$ ), 2.33 (s, 6H, $\text{N}(\text{CH}_3)_2$ ), 1.73 (s, 6H, $\text{CH}_3$ ), 0.86 (s, 9H, $\text{SiC}(\text{CH}_3)_3$ ), 0.09 (s, 9H, $\text{Si}(\text{CH}_3)_3$ ), 0.03 (s, 3H, $\text{Si}(\text{CH}_3)_2$ ), 0.02 (s, 3H, $\text{Si}(\text{CH}_3)_2$ )   |
| $^{13}\text{C}$ NMR (100 MHz, $\text{CDCl}_3$ ), $\delta$ : | 208.5 ( $\text{C}=\text{O}$ ), 166.2 ( $\text{C}(\text{O})\text{CH}=\text{C}$ ), 160.2 ( $\text{CO}_2\text{R}$ ), 132.7 ( $\text{CH}=\text{CH}$ ), 131.5 ( $\text{CH}=\text{CH}$ ), 107.1 ( $\text{C}(\text{CH}_3)_2$ ), 96.3 ( $\text{C}(\text{O})\text{CH}$ ), 78.8, 71.2, 69.9, 42.9, 41.3 ( $\text{N}(\text{CH}_3)_2$ ), 36.4, 25.9 ( $\text{SiC}(\text{CH}_3)_3$ ), 25.8 ( $\text{CH}_3$ ), 25.5 ( $\text{CH}_3$ ), 18.3 ( $\text{SiC}(\text{CH}_3)_3$ ), 2.0 ( $\text{Si}(\text{CH}_3)_3$ ), -5.4 ( $\text{Si}(\text{CH}_3)_2$ ) |
| FTIR (neat), $\text{cm}^{-1}$ :                             | 2954 (m), 1734 (s, $\text{C}=\text{O}$ ), 1623 (w), 1389 (m), 1252 (m), 1121 (m), 841 (s)  |
| HRMS (CI):  | Calc'd for $\text{C}_{25}\text{H}_{46}\text{NO}_6\text{Si}_2$ $[\text{M} + \text{H}]^+$ : 512.2863<br>Found: 512.2863  |
| TLC (30% EtOAc in hexanes), $R_f$ :                         | 0.48   |

**154**

Triisopropylsilyl trifluoromethanesulfonate (245  $\mu\text{L}$ , 913  $\mu\text{mol}$ , 1.1 equiv) was added to an ice-chilled solution of 2-hydroxybenzyl alcohol (103 mg, 830  $\mu\text{mol}$ , 1 equiv) and triethylamine (175  $\mu\text{L}$ , 1.24 mmol, 1.5 equiv) in dichloromethane (5.0 mL). After 25 min, the reaction mixture was poured into water (50 mL), and the product was extracted with a 1:1 mixture of ethyl acetate and hexanes ( $3 \times 50$  mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the crude residue by flash chromatography (10% ethyl acetate–hexanes) gave phenol **154** (215 mg, 92%) as a colorless oil.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 8.27 (s, 1H, OH), 7.18 (t, 1H,  $J = 7.6$  Hz, aryl H), 6.93 (d, 1H,  $J = 7.2$  Hz, aryl H), 6.88 (d, 1H,  $J = 8.0$  Hz, aryl H), 6.81 (t, 1H,  $J = 7.4$  Hz, aryl H), 4.99 (s, 2H,  $\text{CH}_2$ ), 1.18 (m, 3H, SiCH), 1.90 (d, 18H,  $\text{Si}(\text{CH}(\text{CH}_3)_2)_3$ )

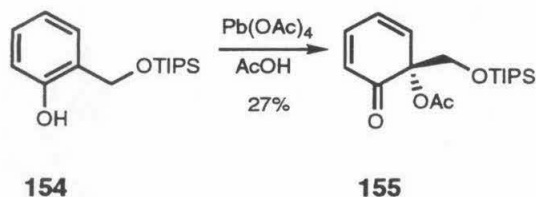
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 156.6, 128.8, 126.5, 124.1, 119.4, 116.6, 66.3, 17.8, 11.7

FTIR (neat),  $\text{cm}^{-1}$ : 3373 (br, OH), 2944 (s), 2867 (s), 1590 (m), 1463 (m), 1244 (m), 1052 (s), 882 (m), 753 (s)

HRMS (CI): Calc'd for  $\text{C}_{16}\text{H}_{29}\text{O}_2\text{Si}$   $[\text{M} + \text{H}]^+$ : 281.1937

Found: 281.1940

TLC (30% EtOAc in hexanes),  $R_f$ : 0.78



Lead(IV) acetate (49 mg, 111  $\mu\text{mol}$ , 1.5 equiv) was added to a solution of phenol **154** (20.8 mg, 74.1  $\mu\text{mol}$ , 1 equiv) in acetic acid (1.5 mL) at 23  $^{\circ}\text{C}$ . After 2 h, saturated aqueous sodium bicarbonate solution (5 mL) was added to the reaction mixture, and the product was extracted with ethyl acetate ( $3 \times 5$  mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash chromatography (5% ethyl acetate–hexanes) afforded the 2,4-cyclohexadienone **155** (6.7 mg, 27%) as a yellow oil.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 7.00 (ddd, 1H,  $J = 9.8, 5.8, 1.9$  Hz,  $\text{C(O)CH=CH}$ ), 6.41 (ddd, 1H,  $J = 9.7, 5.7, 0.9$  Hz,  $\text{CH=CH}$ ), 6.33 (br d, 1H,  $J = 9.8$  Hz,  $\text{CH=CH}$ ), 6.17 (d, 1H,  $J = 9.9$  Hz,  $\text{C(O)CH}$ ), 3.90 (ABq, 2H,  $J = 9.3$  Hz,  $\Delta\nu = 19.9$  Hz,  $\text{CH}_2$ ), 2.09 (s, 3H,  $\text{CH}_3$ ), 1.02 (m, 21H,  $\text{Si}(\text{CH}(\text{CH}_3)_2)_3$ )

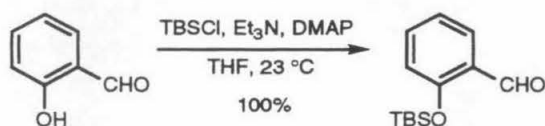
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 197.7, 169.2, 140.7, 139.7, 126.9, 124.3, 80.9, 69.2, 20.4, 17.8, 11.8

FTIR (neat),  $\text{cm}^{-1}$ : 2944 (s), 2866 (s), 1749 (s,  $\text{C=O}$ ), 1680 (s,  $\text{C=O}$ ), 1464 (m), 1369 (m), 1242 (s), 1128 (s)

HRMS (CI): Calc'd for  $\text{C}_{18}\text{H}_{34}\text{NO}_4\text{Si}$  [ $\text{M} + \text{NH}_4$ ] $^{+}$ : 356.2257  
Found: 356.2250

TLC (10% EtOAc in hexanes),  $R_f$ : 0.23



**159**

*tert*-Butyldimethylsilyl chloride (424 mg, 2.82 mmol, 2.0 equiv) was added to a solution of salicylaldehyde (172 mg, 1.41 mmol, 1 equiv) and triethylamine (590  $\mu\text{L}$ , 4.22 mmol, 3.0 equiv) in tetrahydrofuran (8.0 mL) at 23  $^\circ\text{C}$ . 4-Dimethylaminopyridine (1–2 mg) was added to the reaction mixture. After 40 min, the reaction mixture was poured into water (50 mL), and the product was extracted with a 1:1 mixture of ethyl acetate and hexanes ( $3 \times 50$  mL). The combined organic layers were dried over sodium sulfate and were concentrated. Flash chromatography of the residue (4% ethyl acetate–hexanes) provided the protected aldehyde **159** (334 mg, 100% yield) as a colorless oil.

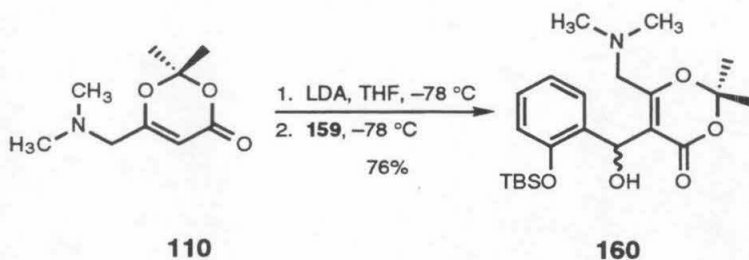
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 10.47 (s, 1H, CHO), 7.81 (dd, 1H,  $J = 7.8, 1.8$  Hz, C-6 aryl H), 7.46 (td, 1H,  $J = 7.8, 1.8$  Hz, C-4 aryl H), 7.03 (t, 1H,  $J = 7.6$  Hz, C-5 aryl H), 6.88 (d, 1H,  $J = 8.3$  Hz, C-3 aryl H), 1.02 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 0.28 (s, 6H,  $\text{Si}(\text{CH}_3)_2$ )

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 190.1 (C=O), 158.9, 135.6, 128.3, 127.3, 121.4, 120.2, 25.7 ( $\text{SiC}(\text{CH}_3)_3$ ), 18.3 ( $\text{SiC}(\text{CH}_3)_3$ ),  $-4.3$  ( $\text{Si}(\text{CH}_3)_2$ )

FTIR (neat),  $\text{cm}^{-1}$ : 2932 (m), 2859 (m), 1690 (s, C=O), 1599 (s), 1479 (s), 1253 (s), 916 (s)

HRMS (EI): Calc'd for  $\text{C}_{13}\text{H}_{21}\text{O}_2\text{Si}$  [ $\text{M} + \text{H}$ ] $^+$ : 237.1311  
Found: 237.1305

TLC (10% EtOAc in hexanes),  $R_f$ : 0.47



*n*-Butyllithium (1.67 mL of a 2.52 M solution in hexanes, 4.20 mmol, 1.20 equiv) was added to a degassed, cooled ( $-78\text{ }^{\circ}\text{C}$ ) solution of diisopropylamine (615  $\mu\text{L}$ , 4.37 mmol, 1.25 equiv) in tetrahydrofuran (12.0 mL). The resulting solution was warmed to  $0\text{ }^{\circ}\text{C}$  for 10 min and was then cooled to  $-78\text{ }^{\circ}\text{C}$ . A solution of amine **110** (648 mg, 3.50 mmol, 1 equiv) in THF (2.0 mL) was added. After 50 min, aldehyde **159** (1.07 g, 4.53 mmol, 1.3 equiv) was added by syringe to the reaction mixture. After an additional 40 min, the reaction mixture was poured into water (60 mL), and the product was extracted with ethyl acetate ( $3 \times 50\text{ mL}$ ). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash chromatography (60% ethyl acetate–hexanes) afforded the aldol adduct **160** (1.12 g, 76%) as a white solid.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 7.59 (d, 1H,  $J = 7.4\text{ Hz}$ , C-6 aryl H), 7.13 (t, 1H,  $J = 7.5\text{ Hz}$ , C-4 aryl H), 6.97 (t, 1H,  $J = 7.4\text{ Hz}$ , C-5 aryl H), 6.82 (d, 1H,  $J = 8.0\text{ Hz}$ , C-3 aryl H), 6.06 (s, 1H, CHOH), 2.70 (ABq, 2H,  $J = 13.6\text{ Hz}$ ,  $\Delta\nu = 184.4\text{ Hz}$ ,  $\text{CH}_2\text{N}(\text{CH}_3)_2$ ), 2.25 (s, 6H,  $\text{N}(\text{CH}_3)_2$ ), 1.65 (s, 3H,  $\text{CH}_3$ ), 1.62 (s, 3H,  $\text{CH}_3$ ), 0.93 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 0.31 (s, 3H,  $\text{Si}(\text{CH}_3)_2$ ), 0.16 (s, 3H,  $\text{Si}(\text{CH}_3)_2$ )

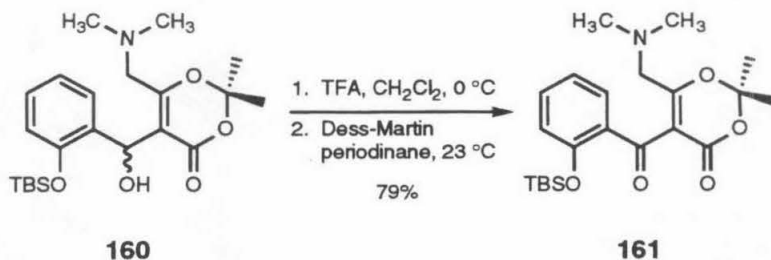
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 163.8 (C(O)C=C), 161.4 (C=O), 152.5, 133.8, 127.8, 126.7, 120.3, 119.4, 113.0 (C(O)C), 105.1 ( $\text{C}(\text{CH}_3)_2$ ), 63.9 (CHOH), 59.1

(CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>), 44.7 (N(CH<sub>3</sub>)<sub>2</sub>), 26.9, 26.3,  
23.5, 18.8, -3.0 (Si(CH<sub>3</sub>)<sub>2</sub>), -3.8 (Si(CH<sub>3</sub>)<sub>2</sub>)

FTIR (neat), cm<sup>-1</sup>: 3190 (w, OH), 2954 (w), 2859 (w), 1731 (s,  
C=O), 1631 (m), 1483 (m), 1395 (m), 1271 (s),  
1030 (m), 837 (m)

HRMS (EI): Calc'd for C<sub>22</sub>H<sub>36</sub>NO<sub>5</sub>Si [M + H]<sup>+</sup>: 422.2363  
Found: 422.2365

TLC (80% EtOAc in hexanes), R<sub>f</sub>: 0.39



Trifluoroacetic acid (26  $\mu\text{L}$ , 339  $\mu\text{mol}$ , 1.1 equiv) was added to an ice-chilled solution of alcohol **160** (130 mg, 308  $\mu\text{mol}$ , 1 equiv) in dichloromethane (5.0 mL). After 5 min, Dess–Martin periodinane (196 mg, 463  $\mu\text{mol}$ , 1.5 equiv) was added to the reaction mixture, and the resulting slurry was stirred vigorously at 23  $^\circ\text{C}$ . After 20 min, the reaction mixture was diluted with diethyl ether (7 mL) and a 1:1 mixture of saturated aqueous sodium bicarbonate solution and saturated aqueous sodium thiosulfate solution (10 mL) and was stirred at 23  $^\circ\text{C}$ . After 30 min, the layers were separated, and the aqueous layer was further extracted with diethyl ether ( $2 \times 10\text{ mL}$ ). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash chromatography (70–80% ethyl acetate–hexanes) provided ketone **161** (102 mg, 79%) as a yellow oil.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 7.49 (dd, 1H,  $J = 7.8, 1.8\text{ Hz}$ , C-6 aryl **H**), 7.34 (td, 1H,  $J = 7.8, 1.8\text{ Hz}$ , C-4 aryl **H**), 6.97 (t, 1H,  $J = 7.4\text{ Hz}$ , C-5 aryl **H**), 6.85 (d, 1H,  $J = 8.2\text{ Hz}$ , C-3 aryl **H**), 3.26 (s, 2H,  $\text{CH}_2\text{N}(\text{CH}_3)_2$ ), 2.26 (s, 6H,  $\text{N}(\text{CH}_3)_2$ ), 1.78 (s, 6H,  $\text{CH}_3$ ), 0.97 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 0.24 (s, 6H,  $\text{Si}(\text{CH}_3)_2$ )

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 189.8 (C=O), 170.5 (C(O)C=C), 158.5 ( $\text{CO}_2\text{R}$ ), 154.6, 132.8, 131.2, 130.4, 120.6, 120.1, 111.7 (C(O)C), 106.6 ( $\text{C}(\text{CH}_3)_2$ ), 58.4 ( $\text{CH}_2\text{N}(\text{CH}_3)_2$ ), 45.4 ( $\text{N}(\text{CH}_3)_2$ ), 25.9, 25.4, 18.5, -4.1

(Si(CH<sub>3</sub>)<sub>2</sub>)

FTIR (neat), cm<sup>-1</sup>:

2933 (w), 2858 (w), 1737 (s, C=O), 1598 (m),  
1481 (m), 1389 (m), 1272 (s), 1205 (m)

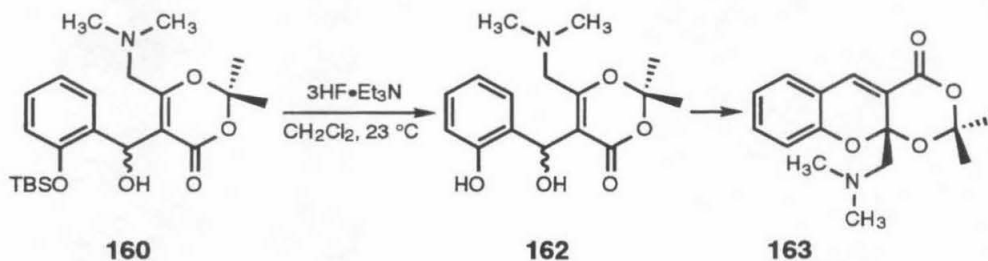
HRMS (EI):

Calc'd for C<sub>22</sub>H<sub>32</sub>NO<sub>5</sub>Si [M - H]<sup>+</sup>: 418.2050

Found: 418.2047

TLC (EtOAc), *R<sub>f</sub>*:

0.34



Triethylamine trihydrofluoride ( $2 \times \sim 10\text{ }\mu\text{L}$ ) was added in two portions to a solution of alcohol **160** (8.7 mg, 20.6  $\mu\text{mol}$ , 1 equiv) in dichloromethane (1.0 mL) at 23  $^\circ\text{C}$ . After the reaction was complete by TLC, the reaction mixture was diluted with water (5 mL) and 10% methanol in dichloromethane (4 mL). The layers were separated, and the aqueous layer was further extracted with 10% methanol in dichloromethane ( $2 \times 3\text{ mL}$ ). The combined organic layers were dried over sodium sulfate and were concentrated. The crude diol **162** was used immediately in subsequent reactions. Over time or under slightly acidic conditions, diol **162** underwent a rearrangement to amine **163**.

#### Amine **163**:

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 7.45 (s, 1H,  $\text{C}(\text{O})\text{C}=\text{CH}$ ), 7.30 (m, 2H, aryl H), 6.99 (m, 2H, aryl H), 2.58 (s, 2H,  $\text{CH}_2\text{N}(\text{CH}_3)_2$ ), 2.28 (s, 6H,  $\text{N}(\text{CH}_3)_2$ ), 1.72 (s, 3H,  $\text{CH}_3$ ), 1.69 (s, 3H,  $\text{CH}_3$ )

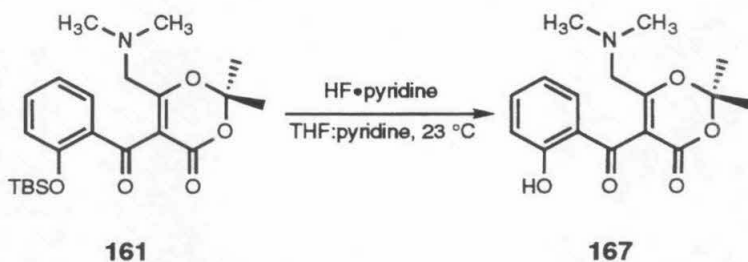
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 163.4, 152.8, 132.6, 131.8, 129.3, 122.1, 119.9, 119.8, 116.6, 104.6, 101.2, 62.9, 46.9, 28.4, 26.9

FTIR (neat),  $\text{cm}^{-1}$ : 2945 (w), 2776 (w), 1739 (s,  $\text{C}=\text{O}$ ), 1644 (m), 1273 (s), 1214 (m), 1123 (m), 1047 (m), 769 (m)

HRMS (CI): Calc'd for  $\text{C}_{16}\text{H}_{20}\text{NO}_4$  [ $\text{M} + \text{H}$ ] $^+$ : 290.1392

Found: 290.1386

TLC (80% EtOAc in hexanes),  $R_f$ : 0.78

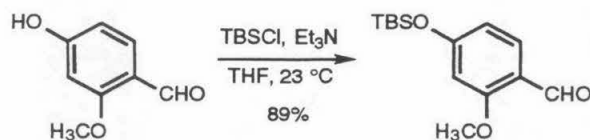


A buffered solution of hydrogen fluoride•pyridine in tetrahydrofuran was prepared by the addition of 70% hydrogen fluoride•pyridine (500  $\mu\text{L}$ ) to a solution of pyridine (2.0 mL) in THF (5.0 mL) at 0  $^\circ\text{C}$ .<sup>76</sup> A 100- $\mu\text{L}$  aliquot was added to a solution of ketone **161** (4.9 mg, 12  $\mu\text{mol}$ , 1 equiv) in tetrahydrofuran (1.0 mL) at 23  $^\circ\text{C}$ . After 35 min, the reaction mixture was diluted with water (5 mL), and the product was extracted with dichloromethane ( $3 \times 5$  mL). The combined organic layers were dried over sodium sulfate and were concentrated to a volume of approximately 500  $\mu\text{L}$ . The pyridine solution was then concentrated to dryness from benzene ( $2 \times 2$  mL) to afford the crude phenol **167** (1.8 mg, ~50%).

$^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ ),  $\delta$ : 7.89 (dd, 1H,  $J = 7.8, 1.6$  Hz, C-6 aryl H), 7.06 (t, 1H,  $J = 7.3$  Hz, C-4 aryl H), 6.93 (d, 1H,  $J = 8.0$  Hz, C-3 aryl H), 6.81 (t, 1H,  $J = 7.6$  Hz, C-5 aryl H), 3.01 (br d, 1H,  $J = 12.9$  Hz,  $\text{CH}_2\text{N}(\text{CH}_3)_2$ ), 2.50 (d, 1H,  $J = 13.2$  Hz,  $\text{CH}_2\text{N}(\text{CH}_3)_2$ ), 2.19 (s, 6H,  $\text{N}(\text{CH}_3)_2$ ), 1.54 (s, 3H,  $\text{CH}_3$ ), 1.45 (s, 3H,  $\text{CH}_3$ )

FTIR (neat),  $\text{cm}^{-1}$ : 3406 (br, OH), 2941 (w), 1682 (s, C=O), 1607 (m), 1427 (m), 1272 (m), 1189 (m), 761 (m)

TLC (EtOAc),  $R_f$ : 0.04

**172**

*tert*-Butyldimethylsilyl chloride (688 mg, 4.57 mmol, 1.4 equiv) was added to a solution of 4-hydroxy-2-methoxybenzaldehyde (497 mg, 3.27 mmol, 1 equiv) and triethylamine (685  $\mu$ L, 4.90 mmol, 1.5 equiv) in tetrahydrofuran (13.0 mL) at 23  $^\circ$ C. After 50 min, the reaction mixture was poured into water (50 mL), and the product was extracted with a 1:1 mixture of ethyl acetate and hexanes (3  $\times$  50 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Flash chromatography of the residue (5% ethyl acetate–hexanes) provided the protected aldehyde **172** (778 mg, 89%) as a white solid.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 10.29 (s, 1H, CHO), 7.74 (d, 1H,  $J$  = 8.5 Hz, C-6 aryl H), 6.47 (dd, 1H,  $J$  = 8.5, 2.2 Hz, C-5 aryl H), 6.39 (d, 1H,  $J$  = 2.1 Hz, C-3 aryl H), 3.88 (s, 3H,  $\text{OCH}_3$ ), 0.99 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 0.26 (s, 6H,  $\text{Si}(\text{CH}_3)_2$ )

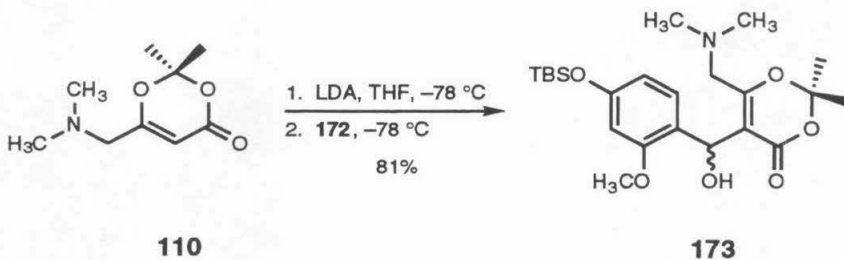
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 187.7 (C=O), 163.4, 162.7, 129.9, 119.2, 112.2, 103.1, 55.2 ( $\text{OCH}_3$ ), 25.3 ( $\text{SiC}(\text{CH}_3)_3$ ), 17.9 ( $\text{SiC}(\text{CH}_3)_3$ ),  $-4.6$  ( $\text{Si}(\text{CH}_3)_2$ )

FTIR (neat),  $\text{cm}^{-1}$ : 2955 (m), 2856 (m), 1668 (m, C=O), 1598 (s), 1167 (s), 779 (s)

HRMS (CI): Calc'd for  $\text{C}_{14}\text{H}_{22}\text{O}_3\text{Si}$   $[\text{M}]^+$ : 266.1338  
Found: 266.1331

TLC (30% EtOAc in hexanes),  $R_f$ : 0.76



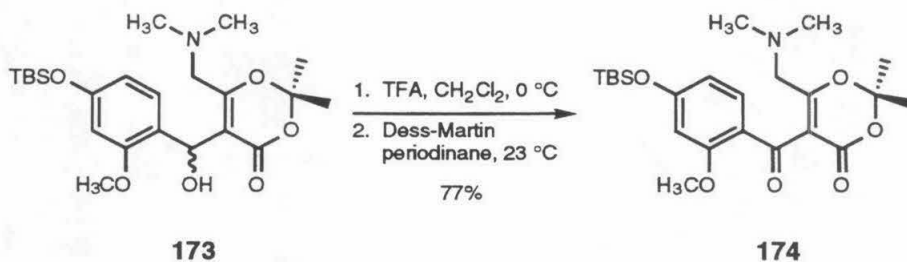


*n*-Butyllithium (555  $\mu\text{L}$  of a 2.35 M solution in hexanes, 1.30 mmol, 1.1 equiv) was added to a degassed, cooled ( $-78\text{ }^{\circ}\text{C}$ ) solution of diisopropylamine (200  $\mu\text{L}$ , 1.42 mmol, 1.2 equiv) in tetrahydrofuran (4.2 mL). The resulting solution was warmed to  $0\text{ }^{\circ}\text{C}$  for 10 min and was then cooled to  $-78\text{ }^{\circ}\text{C}$ . A solution of amine **110** (219 mg, 1.18 mmol, 1 equiv) in THF (0.8 mL) was added to the reaction mixture. After 50 min, aldehyde **172** (377 mg, 1.41 mmol, 1.2 equiv) was added to the reaction mixture. After an additional 45 min, the reaction mixture was poured into water (10 mL), and the product was extracted with ethyl acetate ( $3 \times 10\text{ mL}$ ). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash chromatography (60–70% ethyl acetate–hexanes) afforded the aldol adduct **173** (434 mg, 81%) as an airy white solid.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 7.46 (d, 1H,  $J = 8.3\text{ Hz}$ , C-6 aryl H), 6.47 (dd, 1H,  $J = 8.2, 2.2\text{ Hz}$ , C-5 aryl H), 6.34 (d, 1H,  $J = 2.2\text{ Hz}$ , C-3 aryl H), 5.96 (s, 1H, CHOH), 3.70 (s, 3H,  $\text{OCH}_3$ ), 2.76 (ABq, 2H,  $J = 13.5\text{ Hz}$ ,  $\Delta\nu = 204.0\text{ Hz}$ ,  $\text{CH}_2\text{N}(\text{CH}_3)_2$ ), 2.26 (s, 6H,  $\text{N}(\text{CH}_3)_2$ ), 1.63 (s, 3H,  $\text{CH}_3$ ), 1.57 (s, 3H,  $\text{CH}_3$ ), 0.98 (s, 9H,  $\text{Si}(\text{CH}_3)_3$ ), 0.20 (s, 3H,  $\text{Si}(\text{CH}_3)_2$ ), 0.20 (s, 3H,  $\text{Si}(\text{CH}_3)_2$ )

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 163.1 (C(O)C=C), 161.3 (C=O), 156.1, 155.6, 126.3, 124.4, 113.2, 110.4, 104.9, 103.2, 63.4,

|                                 |  |
|---------------------------------|--|
|                                 | 58.9, 55.0, 44.4 (N(CH <sub>3</sub> ) <sub>2</sub> ), 26.4, 25.5, 23.0, 18.0, -4.6 (Si(CH <sub>3</sub> ) <sub>2</sub> ), -4.6 (Si(CH <sub>3</sub> ) <sub>2</sub> ) |
| FTIR (neat), cm <sup>-1</sup> : | 3183 (w, OH), 2954 (m), 2859 (m), 1730 (s, C=O), 1607 (m), 1499 (m), 1392 (m), 1273 (s), 1202 (s), 1032 (m), 842 (s)   |
| HRMS (FAB):                     | Calc'd for C <sub>23</sub> H <sub>38</sub> NO <sub>6</sub> Si [M + H] <sup>+</sup> : 452.2468<br>Found: 452.2460   |
| TLC (EtOAc), R <sub>f</sub> :   | 0.34   |



Trifluoroacetic acid (7.0  $\mu\text{L}$ , 91.1  $\mu\text{mol}$ , 1.1 equiv) was added to an ice-chilled solution of alcohol **173** (37.4 mg, 82.8  $\mu\text{mol}$ , 1 equiv) in dichloromethane (1.5 mL). After 5 min, Dess–Martin periodinane (56 mg, 132  $\mu\text{mol}$ , 1.6 equiv) was added to the reaction mixture, and the resulting slurry was stirred vigorously at 23  $^\circ\text{C}$ . After 20 min, the reaction mixture was diluted with diethyl ether (4 mL) and a 1:1 mixture of saturated aqueous sodium bicarbonate solution and saturated aqueous sodium thiosulfate solution (5 mL) and was stirred at 23  $^\circ\text{C}$ . After 30 min, the layers were separated, and the aqueous layer was further extracted with diethyl ether (2  $\times$  5 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash chromatography (ethyl acetate) provided ketone **174** (28.7 mg, 77%) as a yellow oil.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 7.71 (d, 1H,  $J$  = 8.6 Hz, C-6 aryl H), 6.47 (dd, 1H,  $J$  = 8.6, 2.2 Hz, C-5 aryl H), 6.34 (d, 1H,  $J$  = 2.1 Hz, C-3 aryl H), 3.77 (s, 3H,  $\text{OCH}_3$ ), 3.32 (s, 2H,  $\text{CH}_2\text{N}(\text{CH}_3)_2$ ), 2.22 (s, 6H,  $\text{N}(\text{CH}_3)_2$ ), 1.81 (s, 6H,  $\text{CH}_3$ ), 0.97 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 0.23 (s, 6H,  $\text{Si}(\text{CH}_3)_2$ )

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 187.7 (C=O), 168.3 (C(O)C=C), 161.6, 160.5, 159.2, 132.9, 122.2, 113.5, 112.5, 106.5, 103.7, 58.2, 55.9, 45.5 ( $\text{N}(\text{CH}_3)_2$ ), 25.6, 25.5, 18.2,  $-4.3$  ( $\text{Si}(\text{CH}_3)_2$ )

FTIR (neat),  $\text{cm}^{-1}$ : 2934 (m), 1737 (s, C=O), 1598 (s), 1388 (m),

1261 (s), 1206 (s), 839 (s)

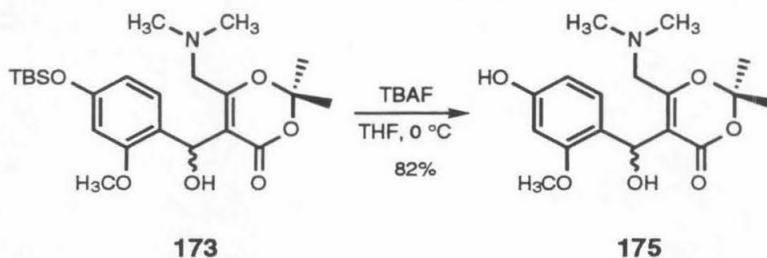
HRMS (FAB):

Calc'd for  $C_{23}H_{35}NO_6Si$   $[M]^+$ : 449.2234

Found: 449.2231

TLC (EtOAc),  $R_f$ :

0.21



Tetrabutylammonium fluoride (55  $\mu$ L of a 1.0 M solution in THF, 55.0  $\mu$ mol, 1.1 equiv) was added to an ice-chilled solution of alcohol **173** (22.6 mg, 50.0  $\mu$ mol, 1 equiv) in tetrahydrofuran (2.0 mL). After 15 min, the reaction mixture was diluted with water (5 mL), and the product was extracted with dichloromethane ( $3 \times 5$  mL). The combined organics were dried over sodium sulfate and were concentrated. Purification of the residue by flash chromatography (5% methanol–dichloromethane) provided diol **175** (13.8 mg, 82%) as a white solid.

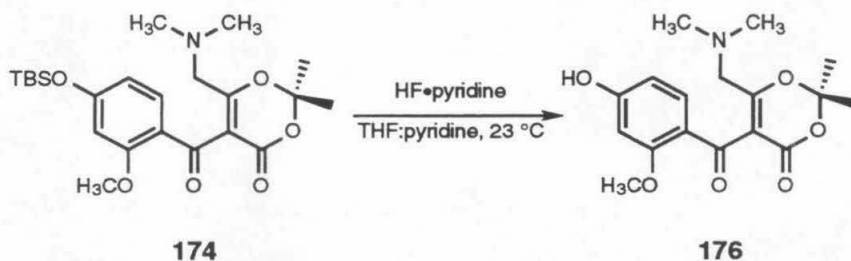
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 7.44 (d, 1H,  $J = 8.2$  Hz, C-6 aryl H), 6.44 (dd, 1H,  $J = 8.2, 2.3$  Hz, C-5 aryl H), 6.38 (d, 1H,  $J = 2.3$  Hz, C-3 aryl H), 5.99 (s, 1H, CHOH), 3.67 (s, 3H,  $\text{OCH}_3$ ), 2.80 (ABq, 2H,  $J = 13.6$  Hz,  $\Delta\nu = 209.3$  Hz,  $\text{CH}_2\text{N}(\text{CH}_3)_2$ ), 2.27 (s, 6H,  $\text{N}(\text{CH}_3)_2$ ), 1.64 (s, 3H,  $\text{CH}_3$ ), 1.58 (s, 3H,  $\text{CH}_3$ )

$^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{OD}$ ),  $\delta$ : 165.7 (C(O)C=C), 163.6 (C=O), 159.3, 157.9, 127.7, 123.2, 114.1, 107.1, 106.9, 99.8, 64.3, 58.9, 55.7, 44.9 ( $\text{N}(\text{CH}_3)_2$ ), 26.8 ( $\text{CH}_3$ ), 23.4 ( $\text{CH}_3$ )

FTIR (neat),  $\text{cm}^{-1}$ : 3194 (w, OH), 1725 (s, C=O), 1632 (m), 1456 (m), 1275 (m), 1204 (m), 1024 (s), 835 (m)

HRMS (CI): Calc'd for  $\text{C}_{17}\text{H}_{24}\text{NO}_6$  [ $\text{M} + \text{H}$ ] $^+$ : 338.1603  
Found: 338.1598

TLC (EtOAc),  $R_f$ : 0.14

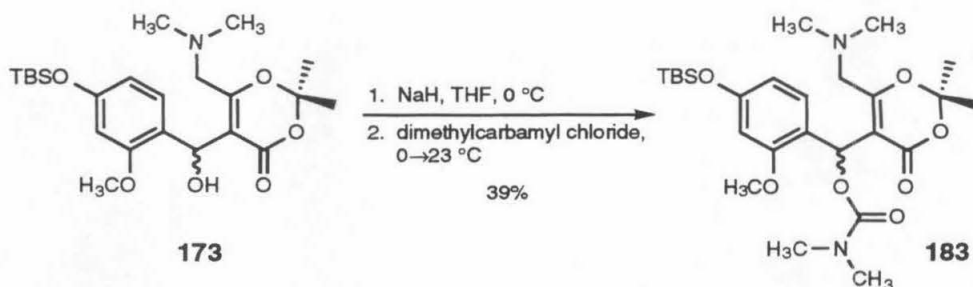


A buffered solution of hydrogen fluoride•pyridine in tetrahydrofuran was prepared by the addition of 70% hydrogen fluoride•pyridine (500  $\mu\text{L}$ ) to a solution of pyridine (2.0 mL) in THF (5.0 mL) at 0  $^\circ\text{C}$ .<sup>76</sup> A 130- $\mu\text{L}$  aliquot was added to a solution of ketone **174** (6.3 mg, 14  $\mu\text{mol}$ , 1 equiv) in tetrahydrofuran (1.0 mL) at 23  $^\circ\text{C}$ . After 15 min, the reaction mixture was diluted with water (5 mL), and the product was extracted with dichloromethane (3  $\times$  5 mL). The combined organic layers were dried over sodium sulfate and were concentrated to a volume of approximately 500  $\mu\text{L}$ . The solution (pyridine) was then concentrated to dryness from benzene (2  $\times$  2 mL) to afford the crude phenol **176** (1.9 mg, ~40%).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 7.72 (d, 1H,  $J$  = 8.6 Hz, C-6 aryl H), 6.41 (dd, 1H,  $J$  = 8.6, 2.2 Hz, C-5 aryl H), 6.30 (d, 1H,  $J$  = 2.2 Hz, C-3 aryl H), 3.75 (s, 3H,  $\text{OCH}_3$ ), 3.37 (s, 2H,  $\text{CH}_2\text{N}(\text{CH}_3)_2$ ), 2.26 (s, 6H,  $\text{N}(\text{CH}_3)_2$ ), 1.83 (s, 6H,  $\text{CH}_3$ )

FTIR (neat),  $\text{cm}^{-1}$ : 2927 (w), 1723 (s,  $\text{C}=\text{O}$ ), 1609 (m), 1571 (m), 1374 (m), 1205 (s), 1112 (m), 836 (m)

TLC (EtOAc),  $R_f$ : 0.07



Sodium hydride (7.7 mg of a 60% dispersion in mineral oil, 192  $\mu\text{mol}$ , 5.5 equiv) was added to an ice-chilled solution of alcohol **173** (15.8 mg, 35  $\mu\text{mol}$ , 1 equiv) in tetrahydrofuran (1.5 mL). After 55 min, dimethylcarbamyl chloride (39  $\mu\text{L}$ , 420  $\mu\text{mol}$ , 12.0 equiv) was added, and the reaction mixture was stirred at 0  $^\circ\text{C}$  for 20 min and was then warmed to 23  $^\circ\text{C}$ . After 2.5 h, the reaction mixture was quenched upon the addition of water (5 mL), and the product was extracted with dichloromethane ( $3 \times 5$  mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash chromatography (5% methanol–dichloromethane) afforded carbamate **183** (7.1 mg, 39%) as a yellow oil, along with alcohol **173** (4.5 mg, 28%).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 7.41 (d, 1H,  $J = 8.4$  Hz, C-6 aryl H), 6.90 (s, 1H, CHOR), 6.44 (dd, 1H,  $J = 8.4, 2.2$  Hz, C-5 aryl H), 6.32 (d, 1H,  $J = 2.2$  Hz, C-3 aryl H), 3.74 (s, 3H,  $\text{OCH}_3$ ), 3.44 (ABq, 2H,  $J = 14.8$  Hz,  $\Delta\nu = 48.0$  Hz,  $\text{CH}_2\text{N}(\text{CH}_3)_2$ ), 3.02 (br, 3H,  $\text{C}(\text{O})\text{N}(\text{CH}_3)_2$ ), 2.92 (br, 3H,  $\text{C}(\text{O})\text{N}(\text{CH}_3)_2$ ), 2.20 (s, 6H,  $\text{CH}_2\text{N}(\text{CH}_3)_2$ ), 1.69 (s, 3H,  $\text{CH}_3$ ), 1.61 (s, 3H,  $\text{CH}_3$ ), 0.97 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 0.19 (s, 6H,  $\text{Si}(\text{CH}_3)_2$ )

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 165.8, 159.7, 156.5, 156.2, 155.5, 128.2,

120.4, 111.3, 107.9, 105.3, 103.0, 66.4, 57.3,  
55.2, 45.5, 36.5, 36.0, 25.7, 25.3, 24.7, 18.2,  
−4.4

FTIR (neat),  $\text{cm}^{-1}$ :

2935 (m), 1733 (s, C=O), 1706 (s, C=O), 1388  
(s), 1201 (s), 1179 (s), 980 (m), 842 (s)

HRMS (FAB):

Calc'd for  $\text{C}_{26}\text{H}_{43}\text{N}_2\text{O}_7\text{Si}$   $[\text{M} + \text{H}]^+$ : 523.2839

Found: 523.2823

TLC (EtOAc),  $R_f$ :

0.14



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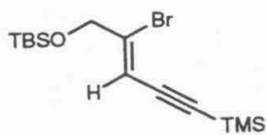
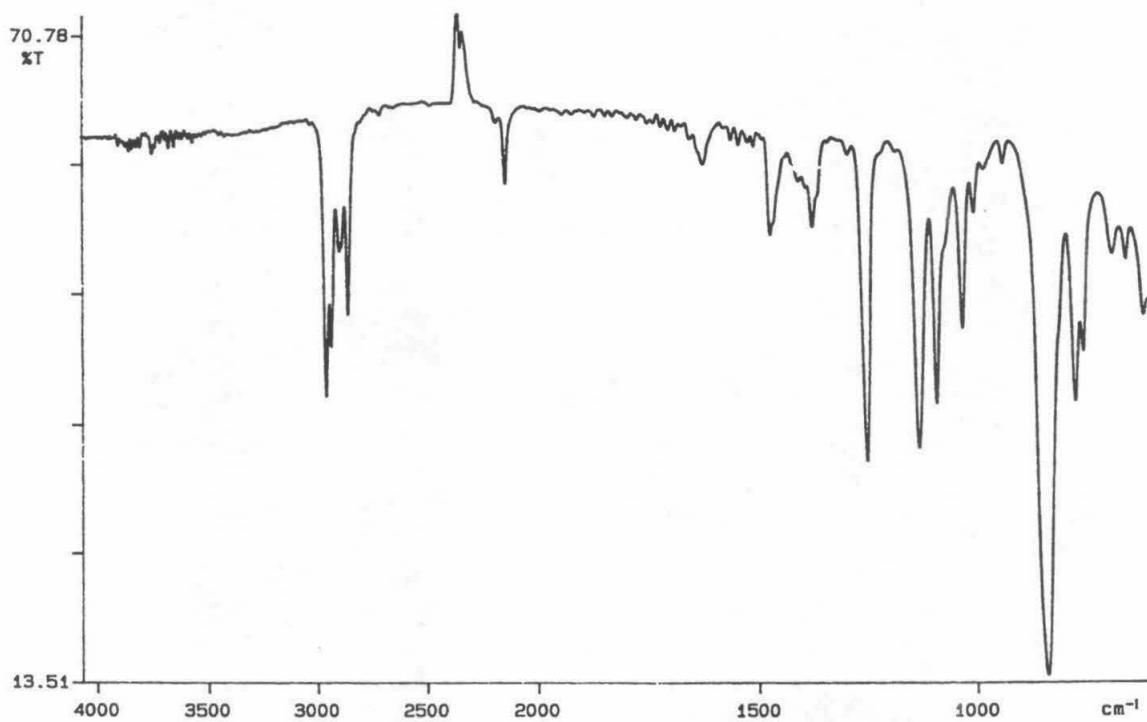
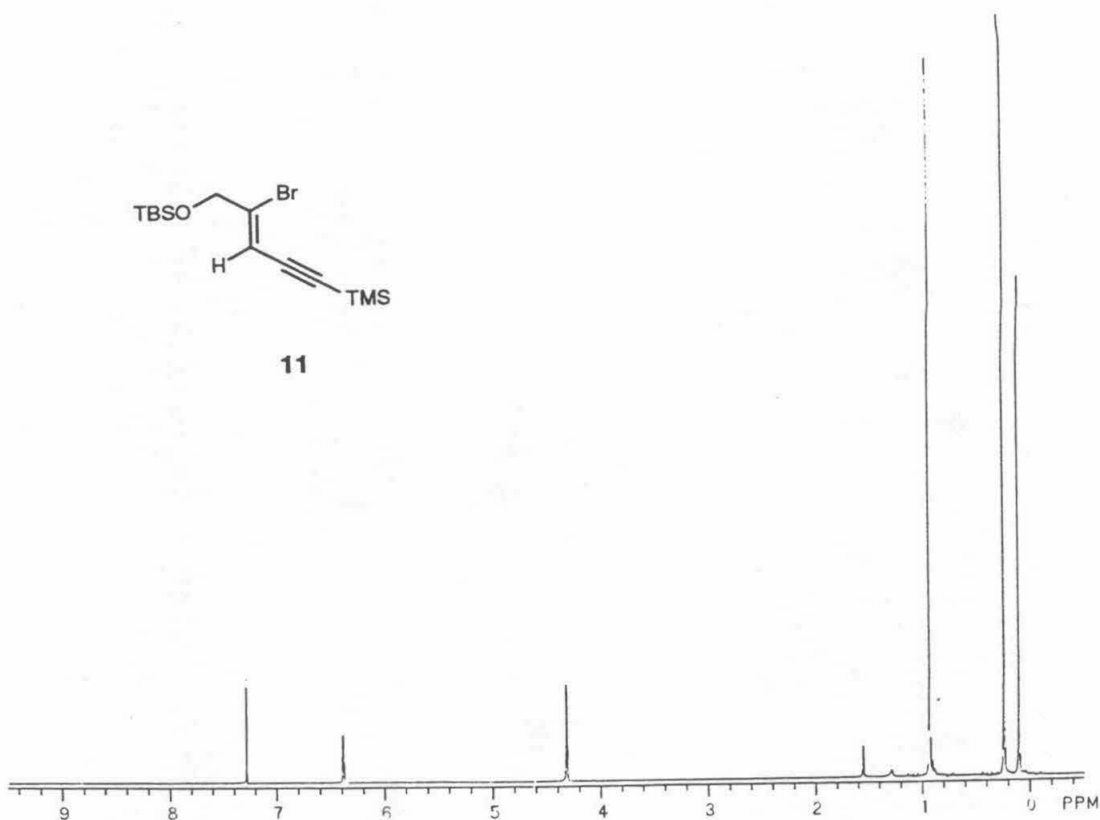
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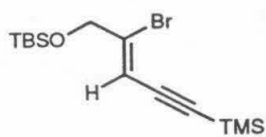
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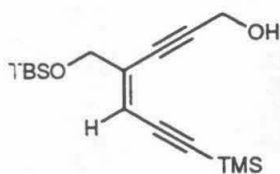
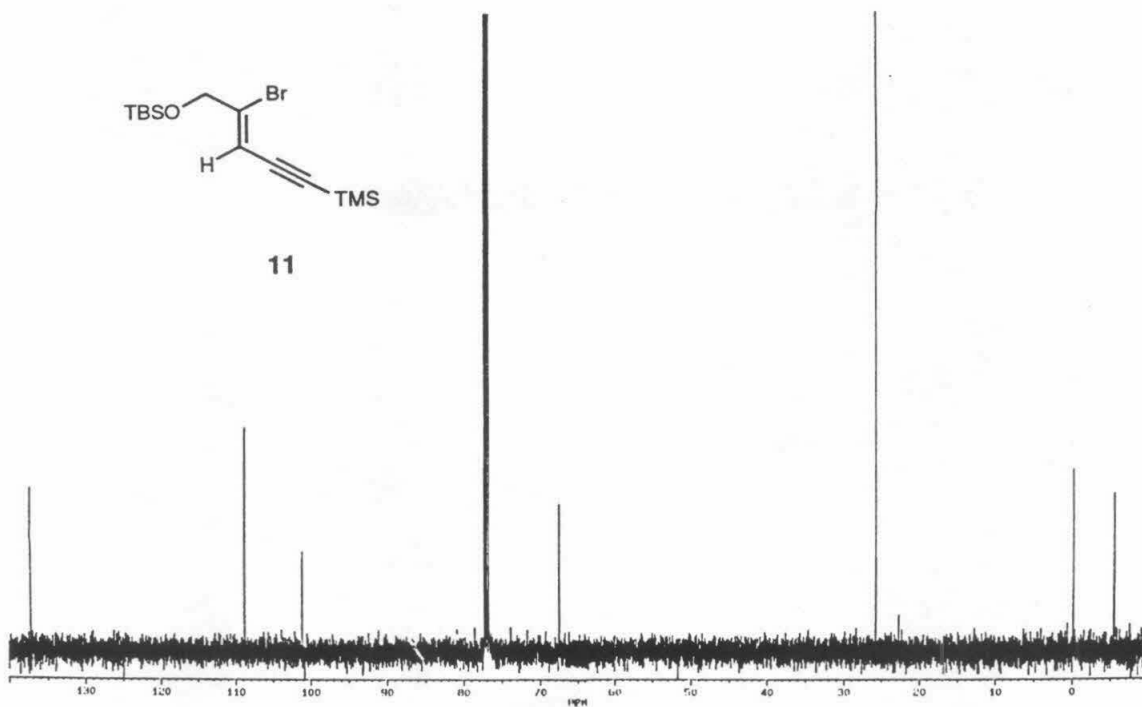
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**Appendix**  
**Catalog of Spectra**

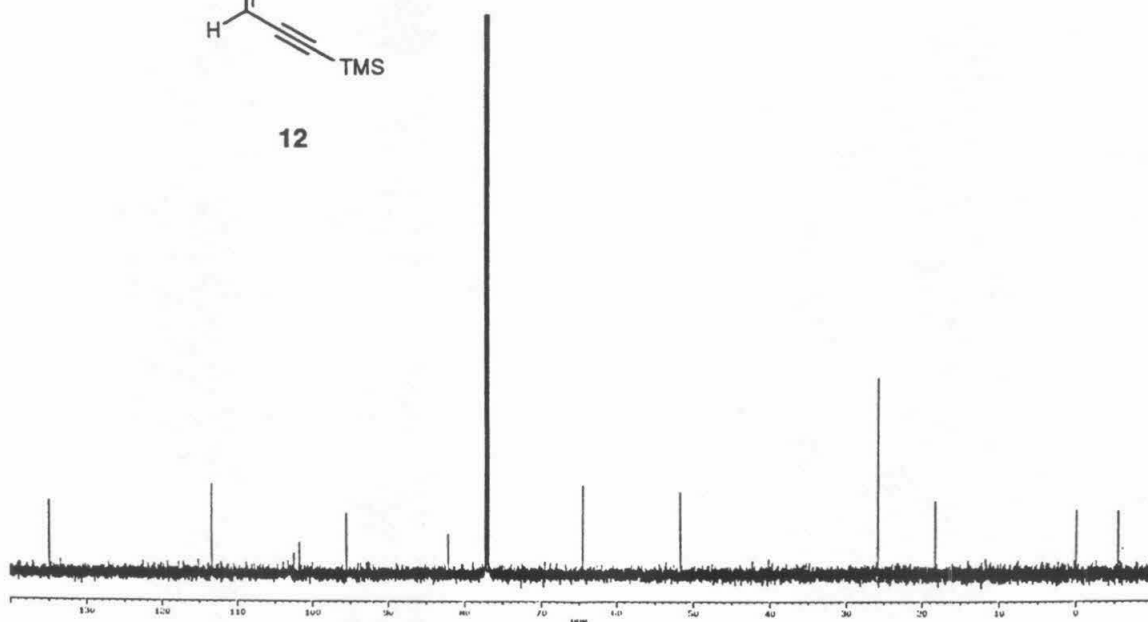
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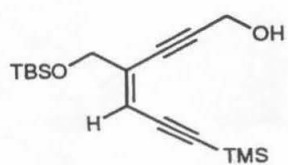
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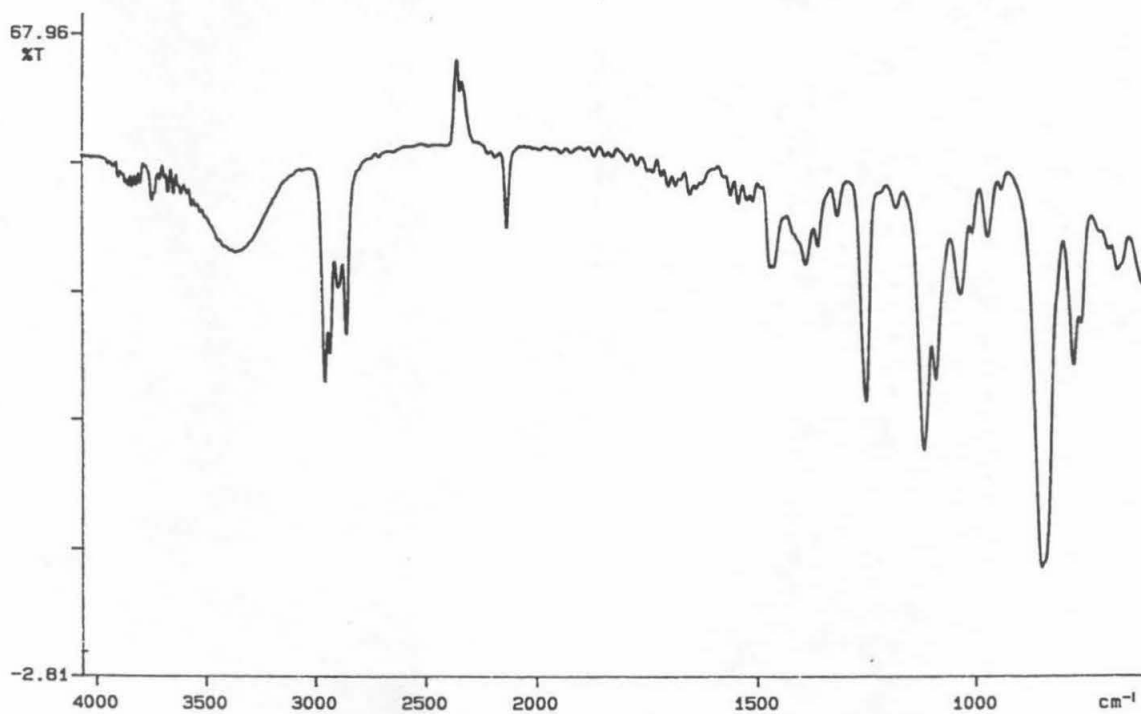
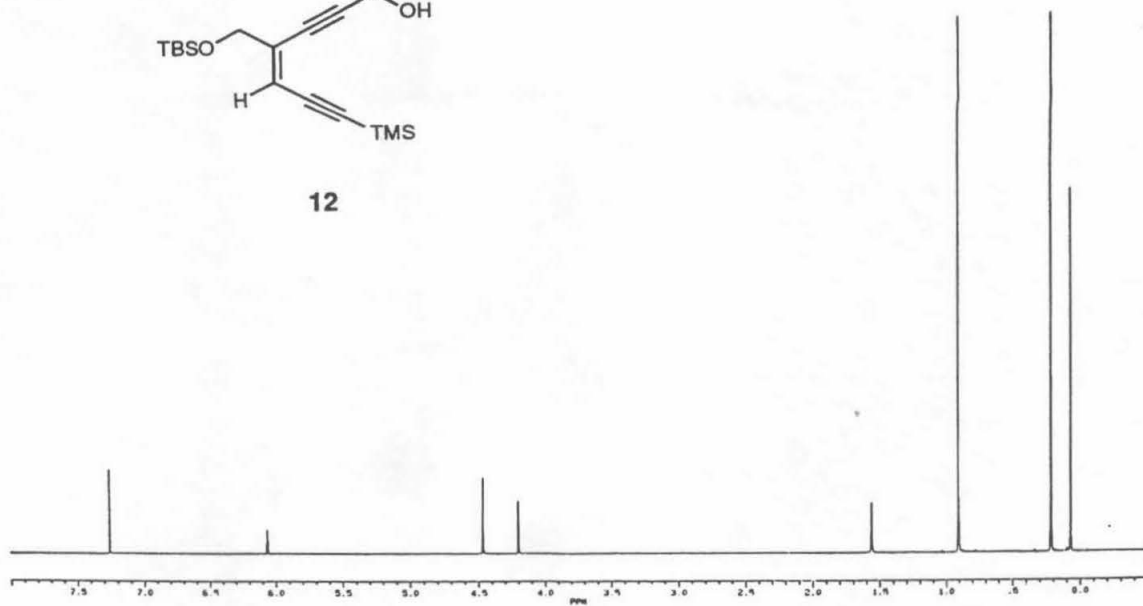
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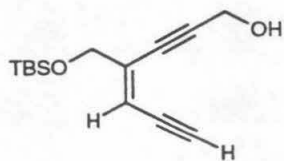
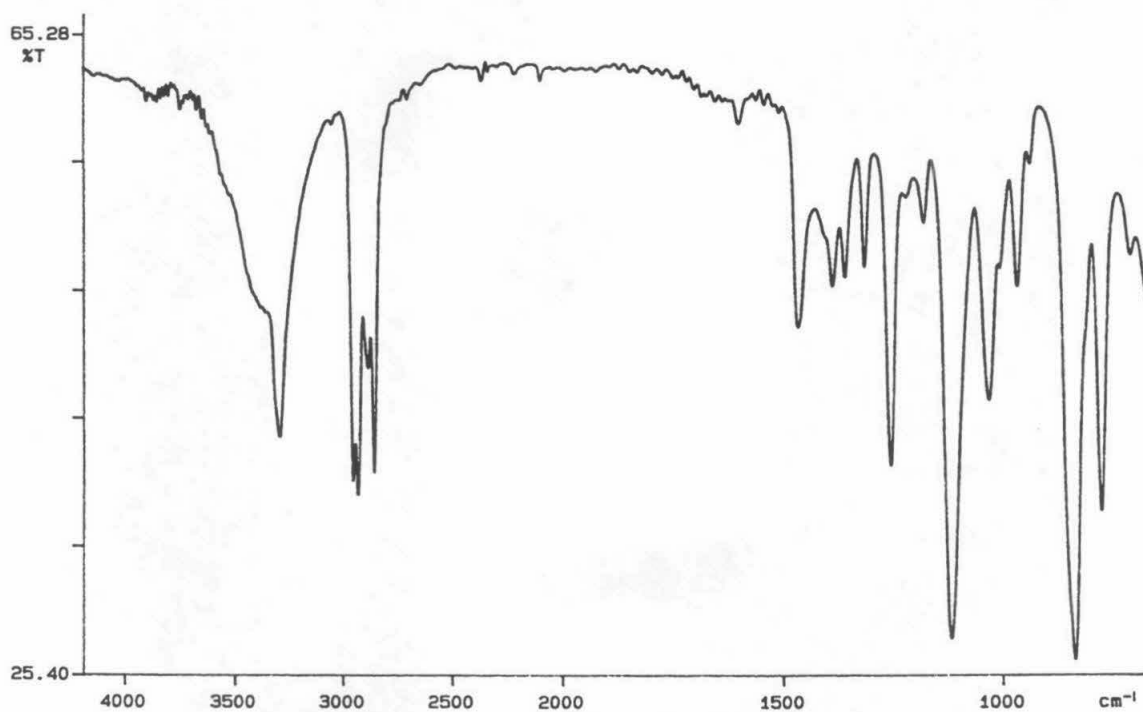
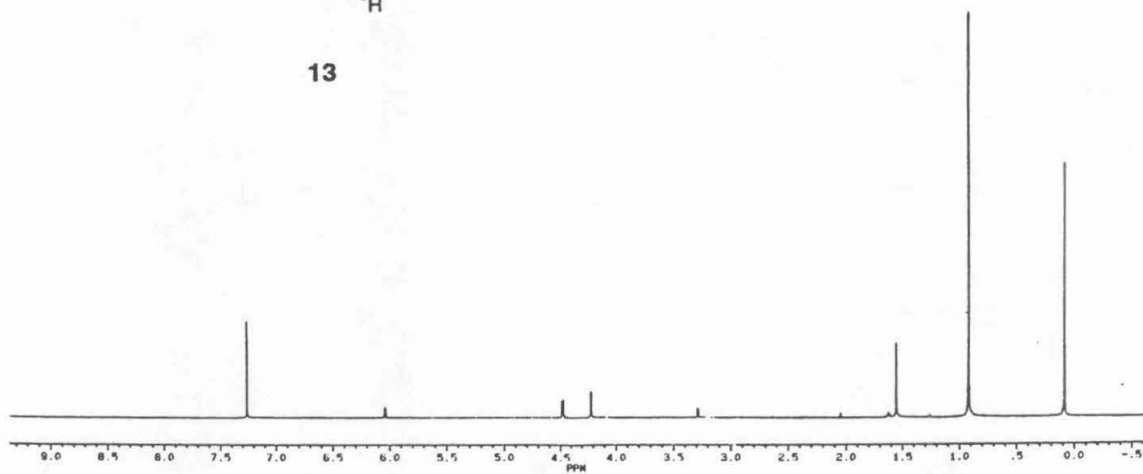


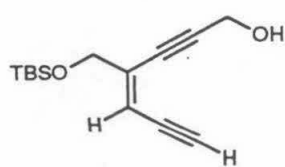
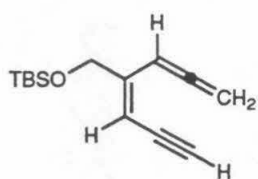
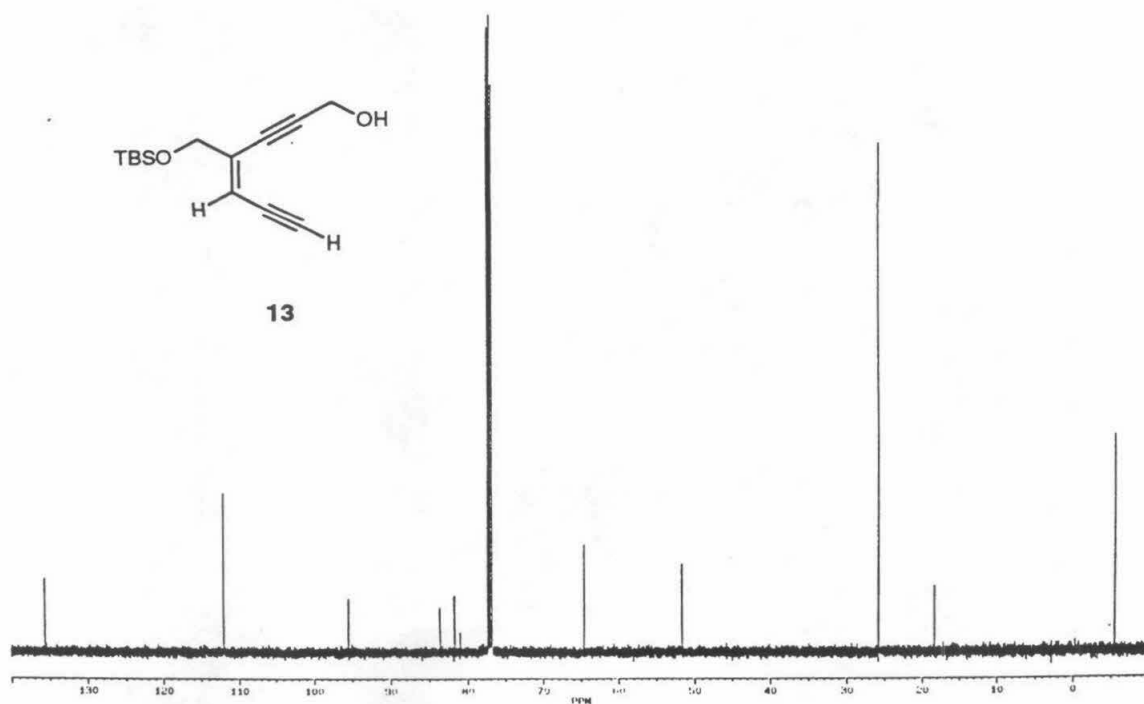
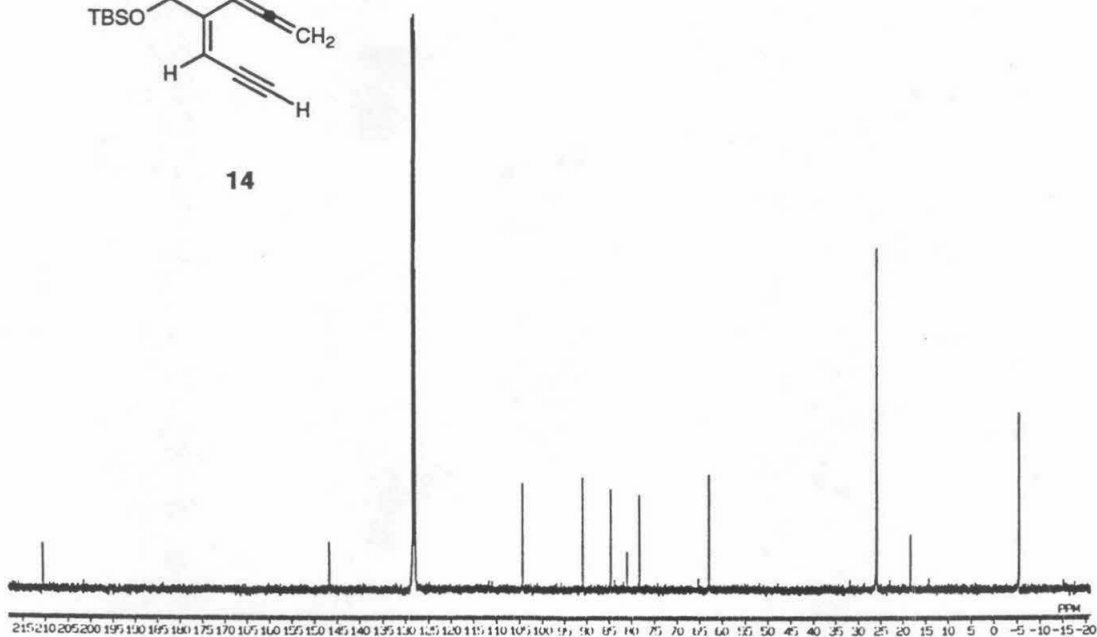


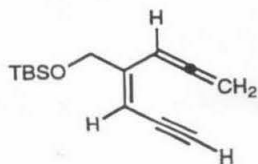


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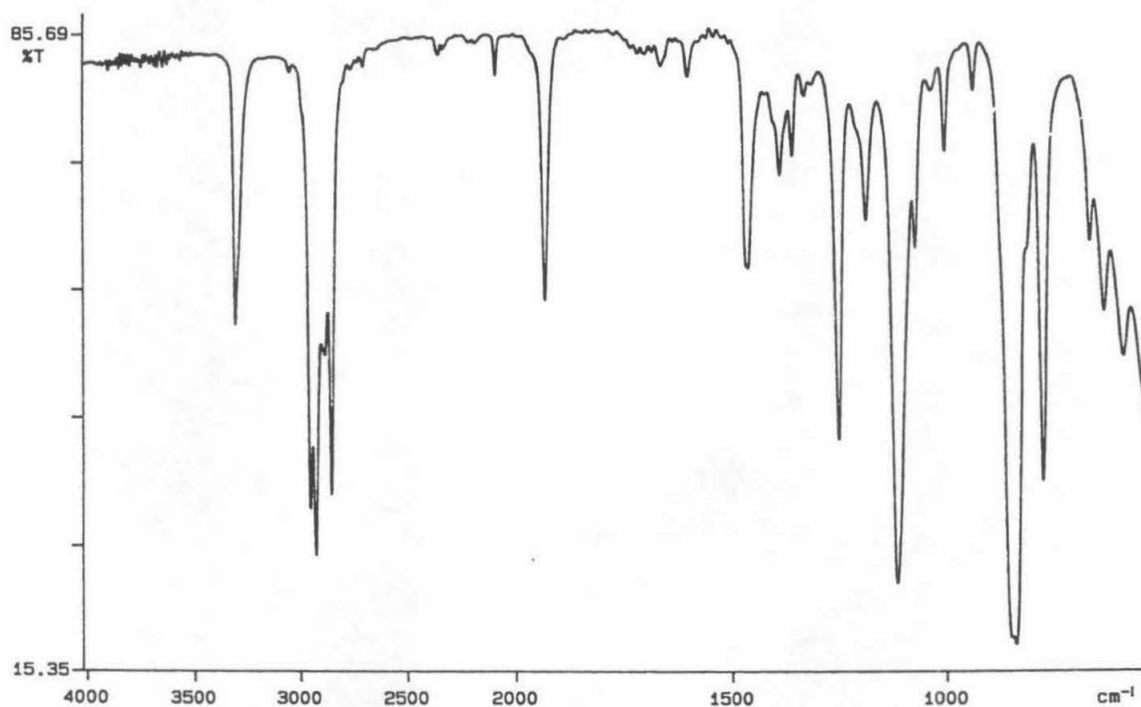
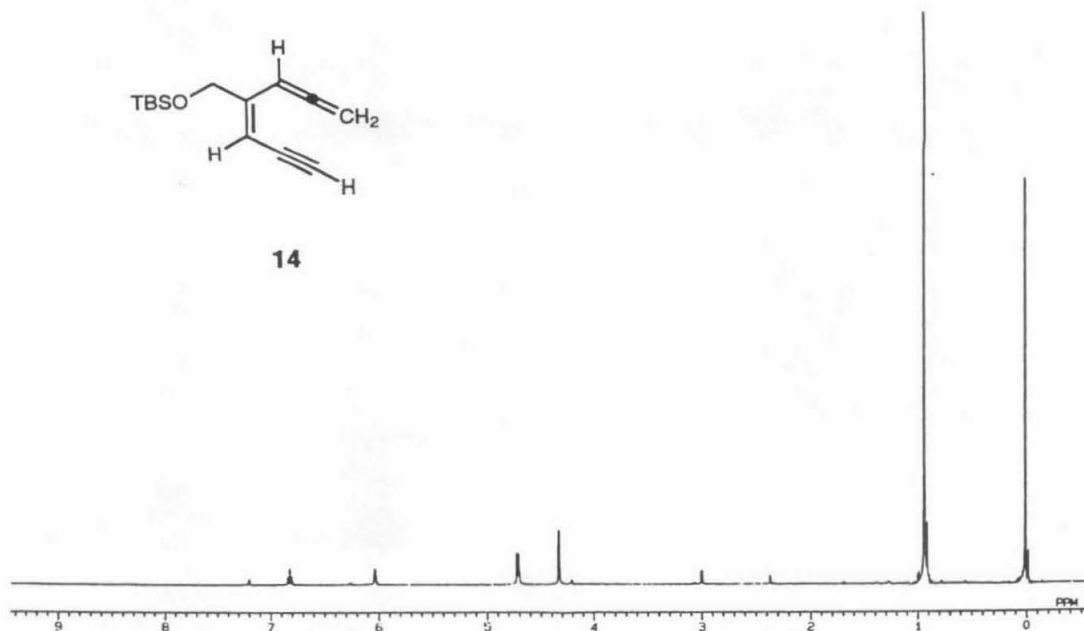


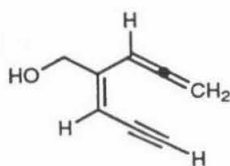
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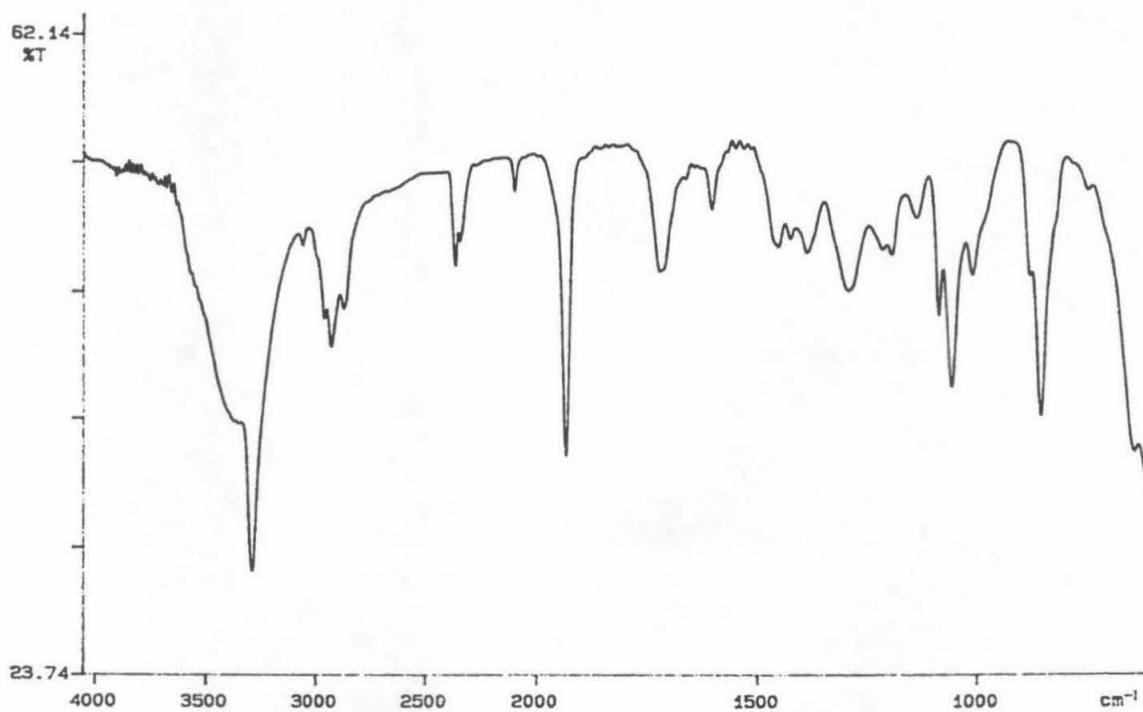
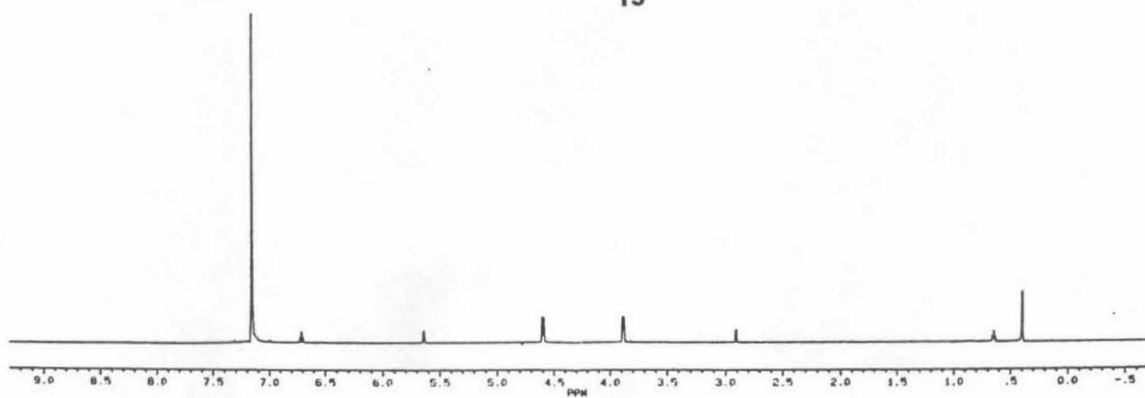


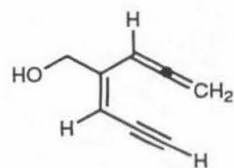
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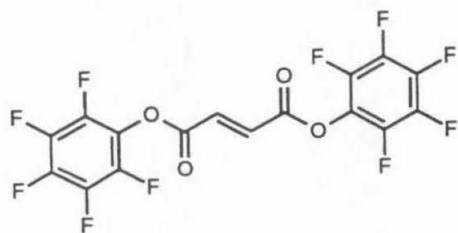
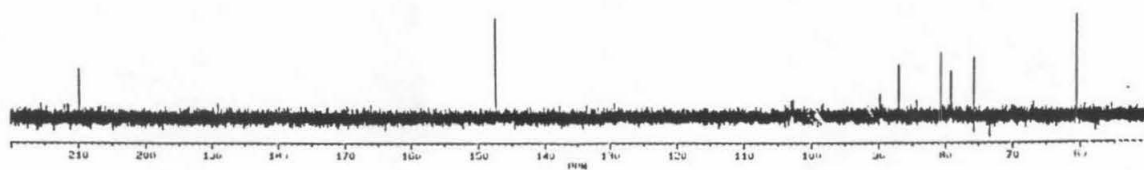


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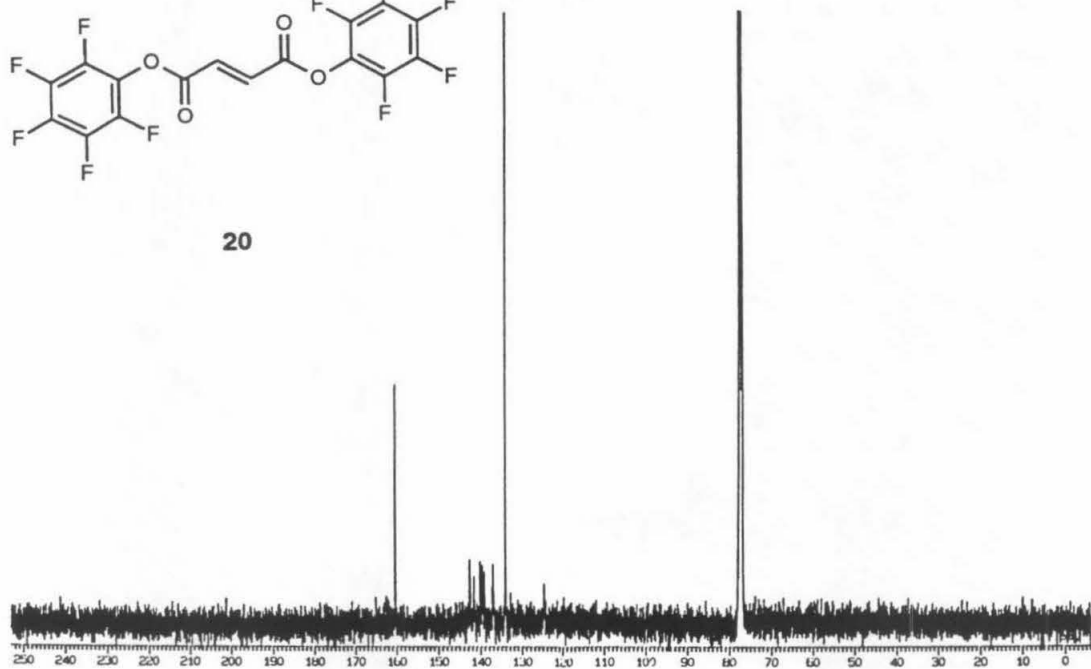


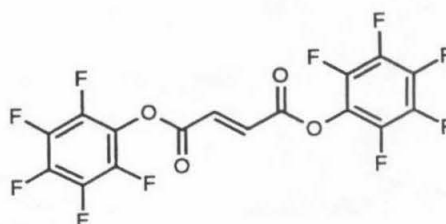


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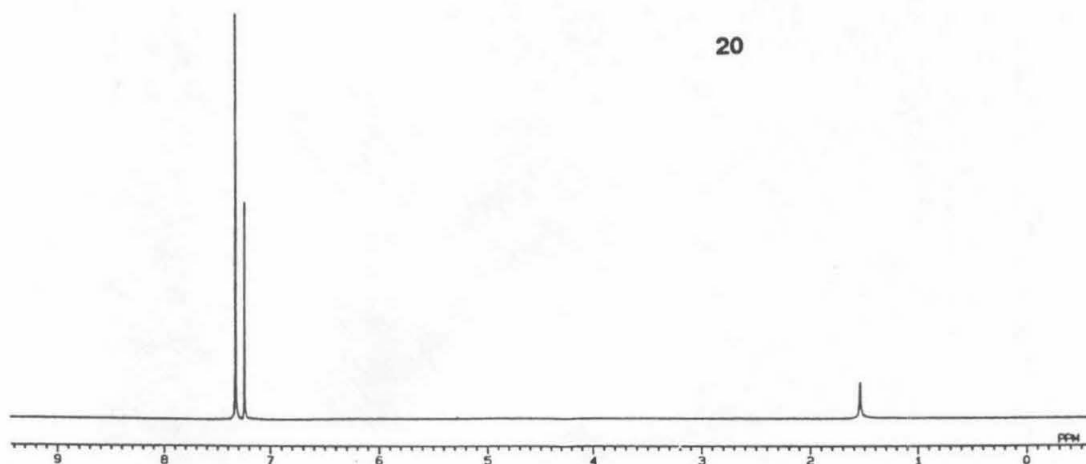
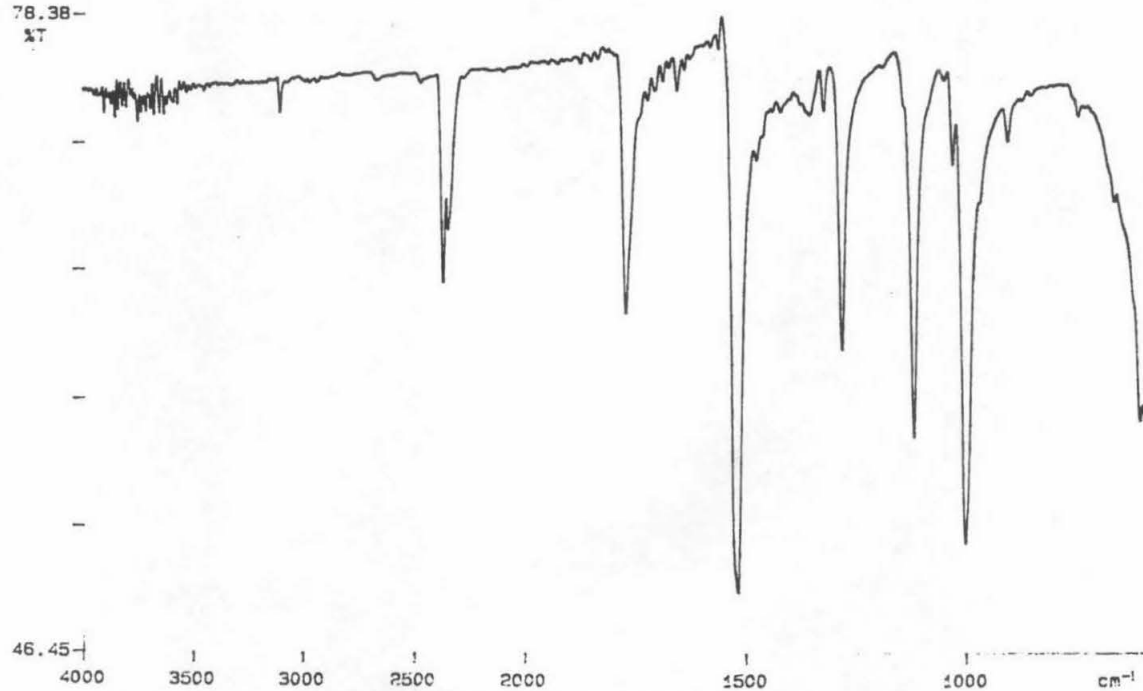


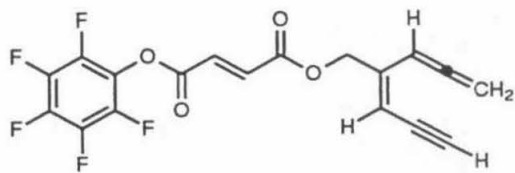
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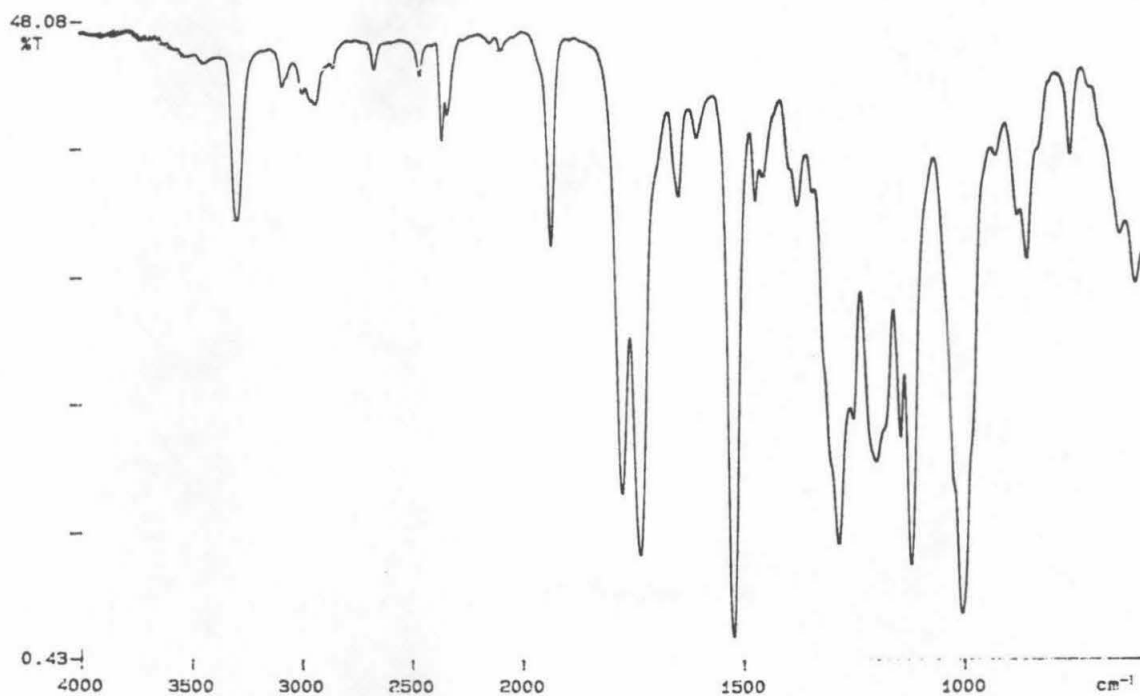
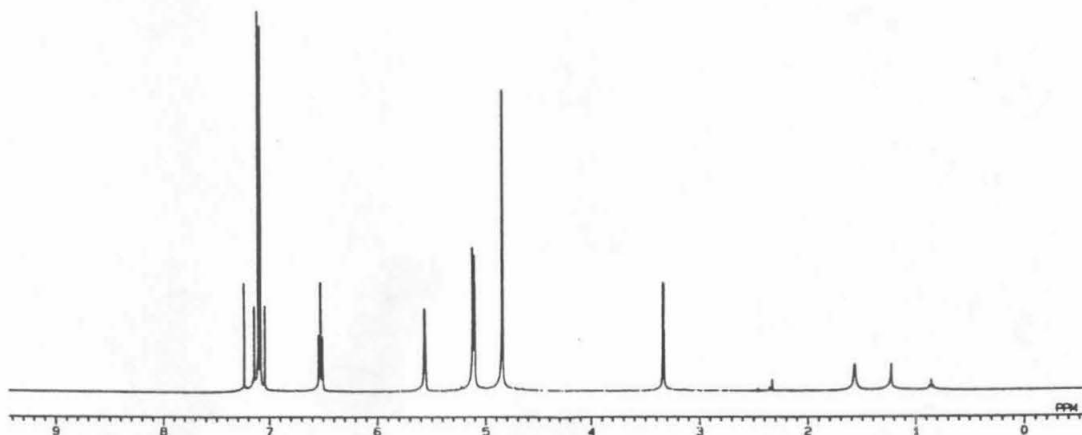


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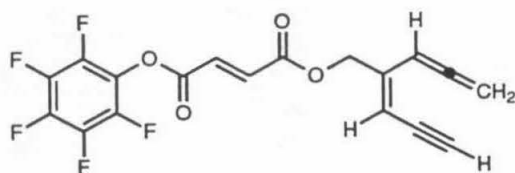
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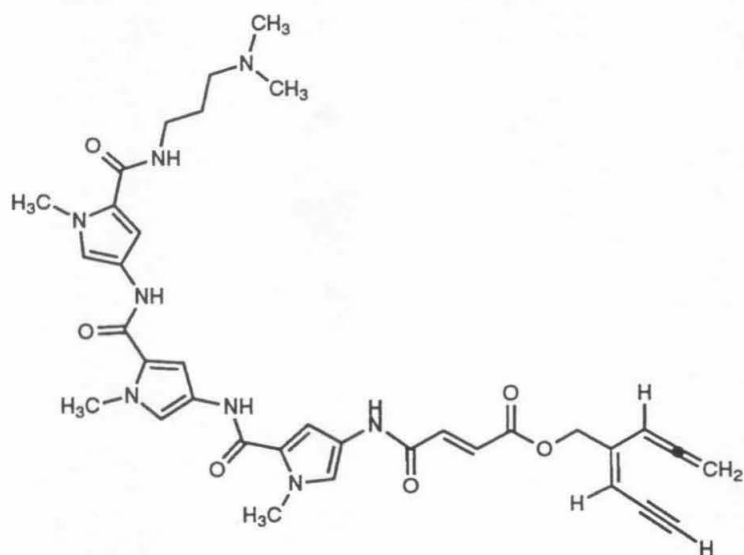
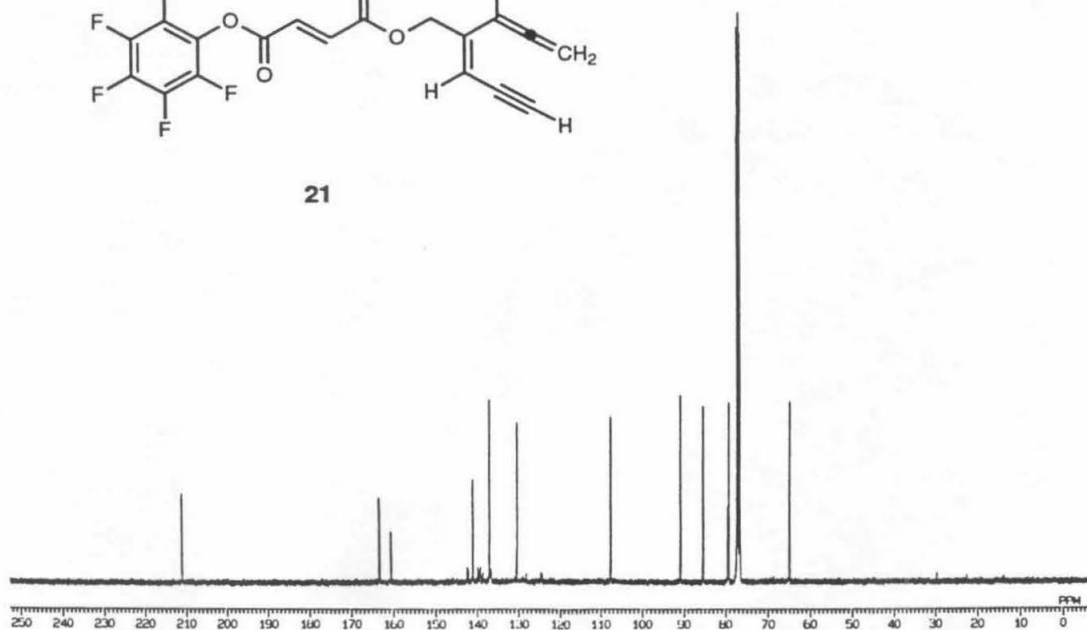
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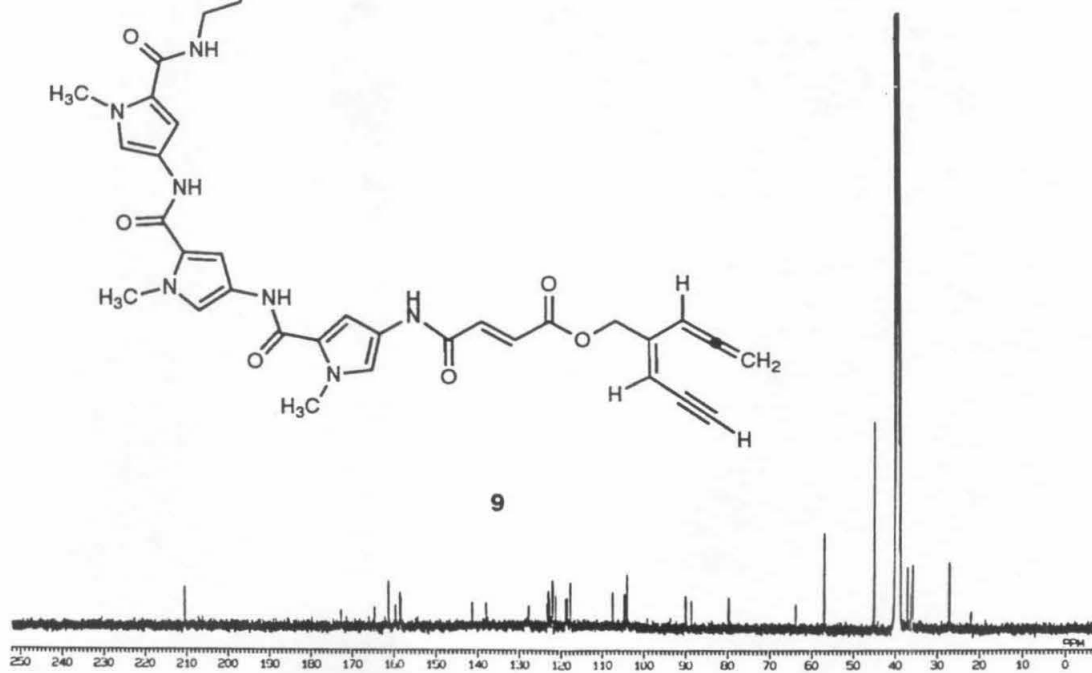


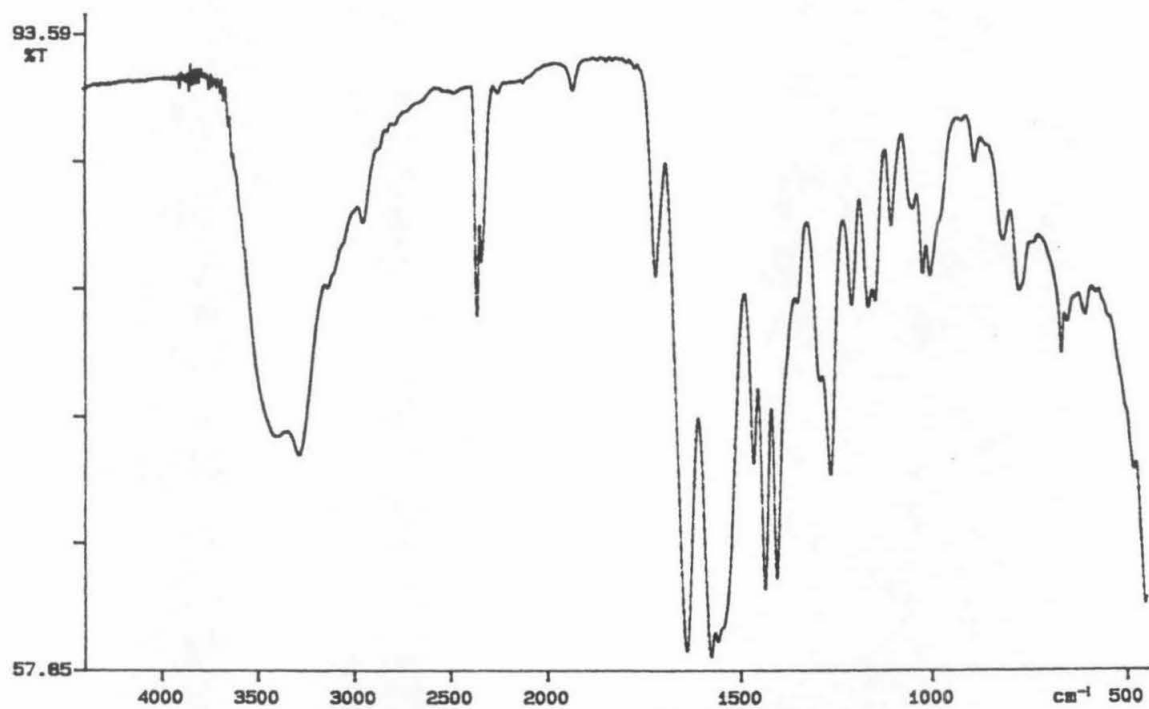
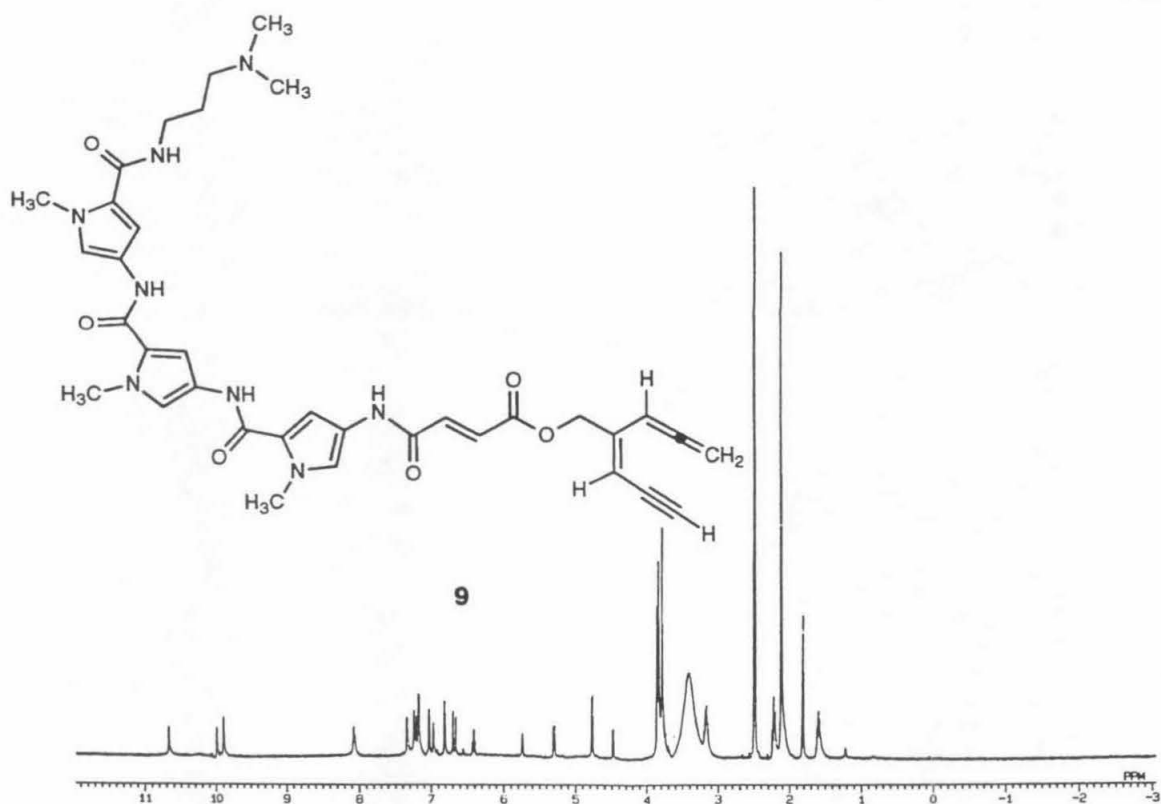


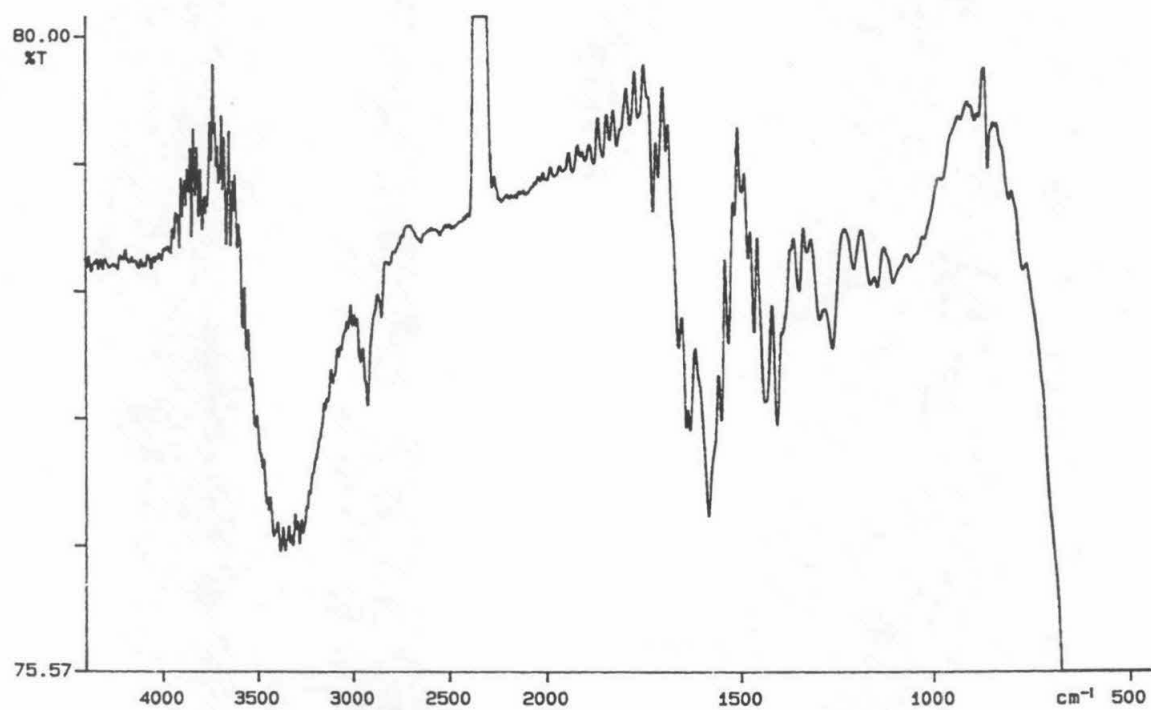
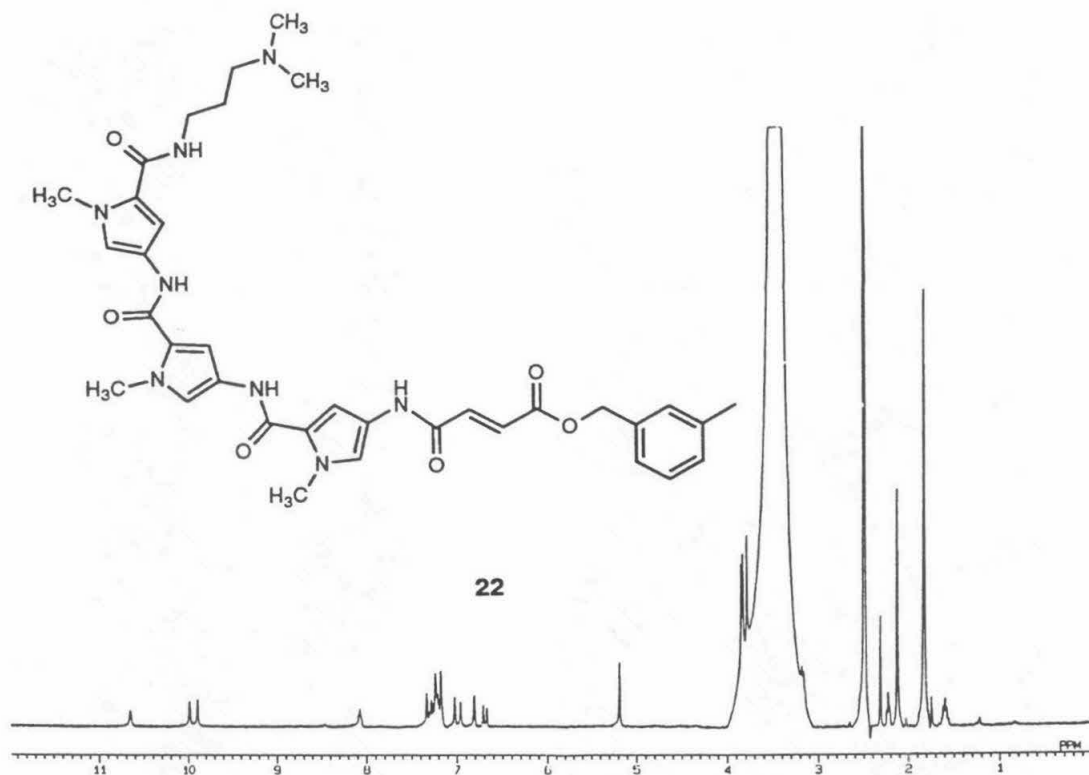
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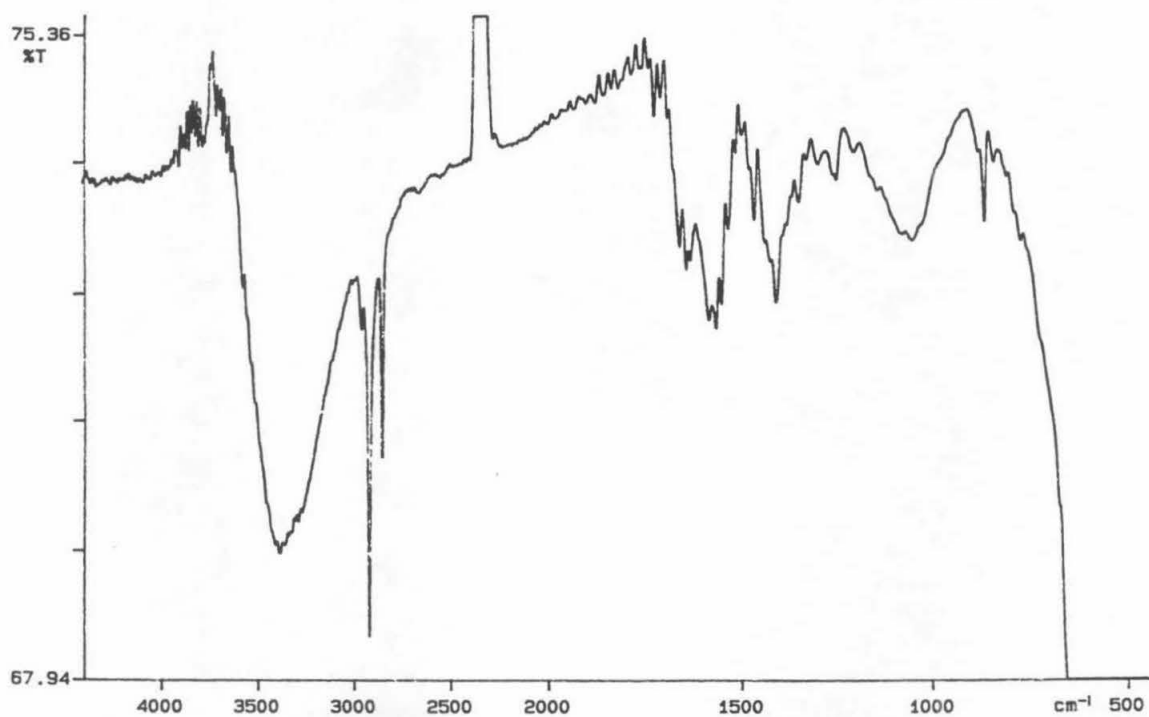
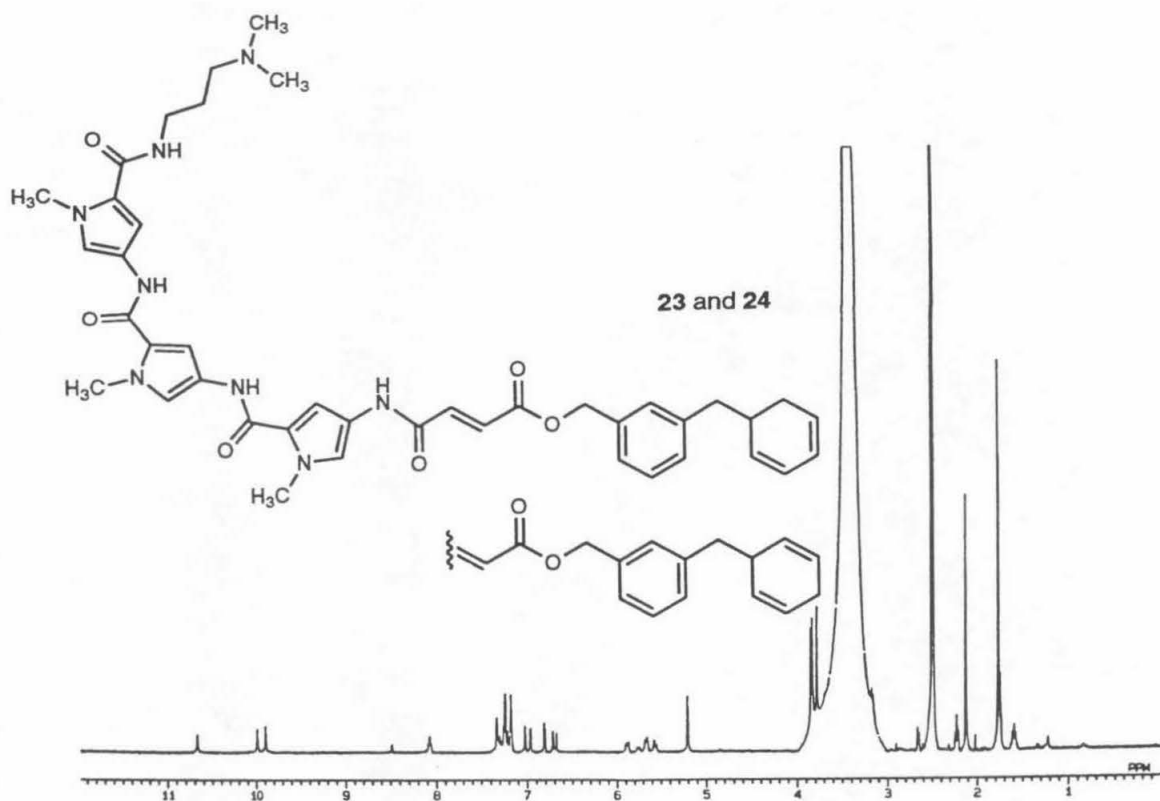


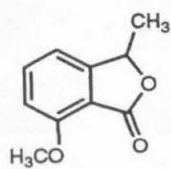
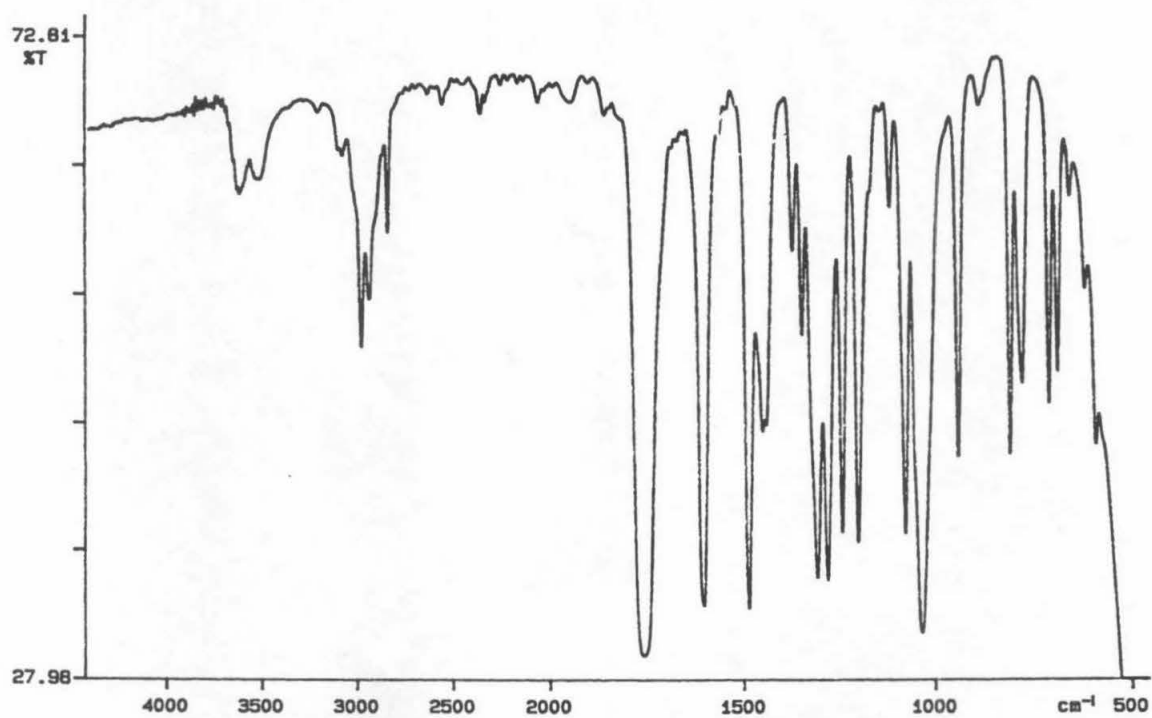
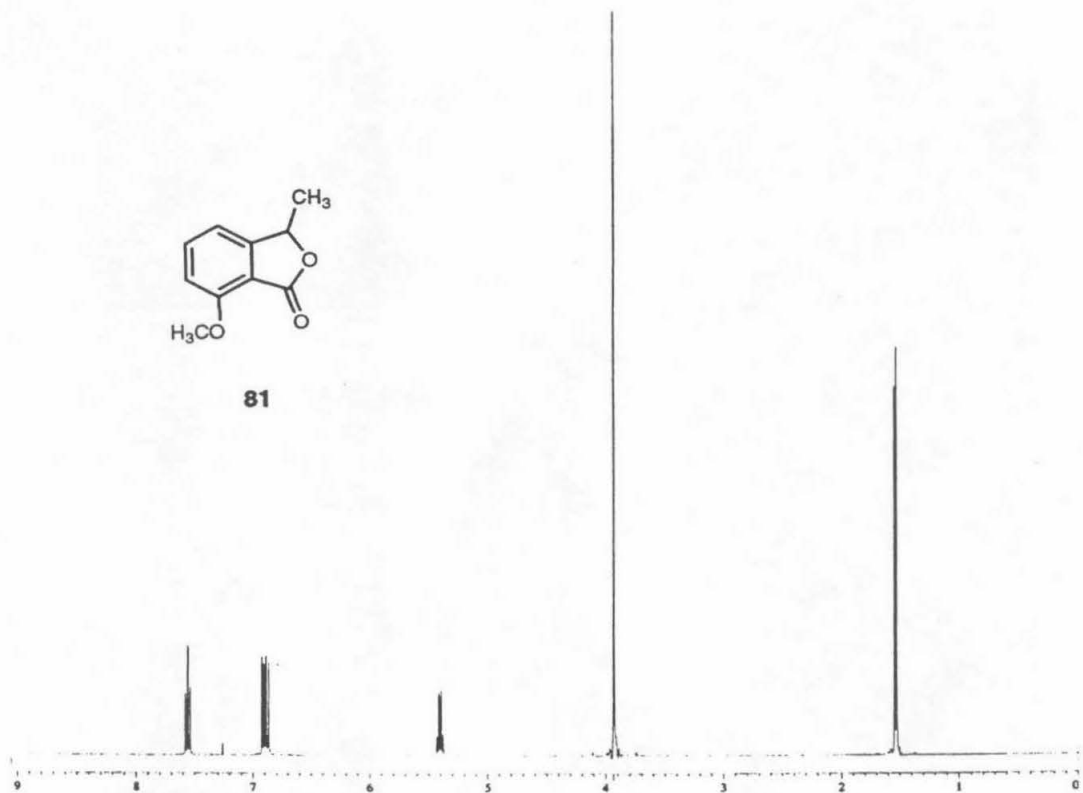
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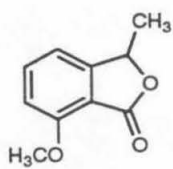




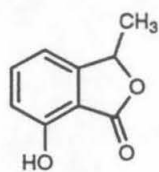
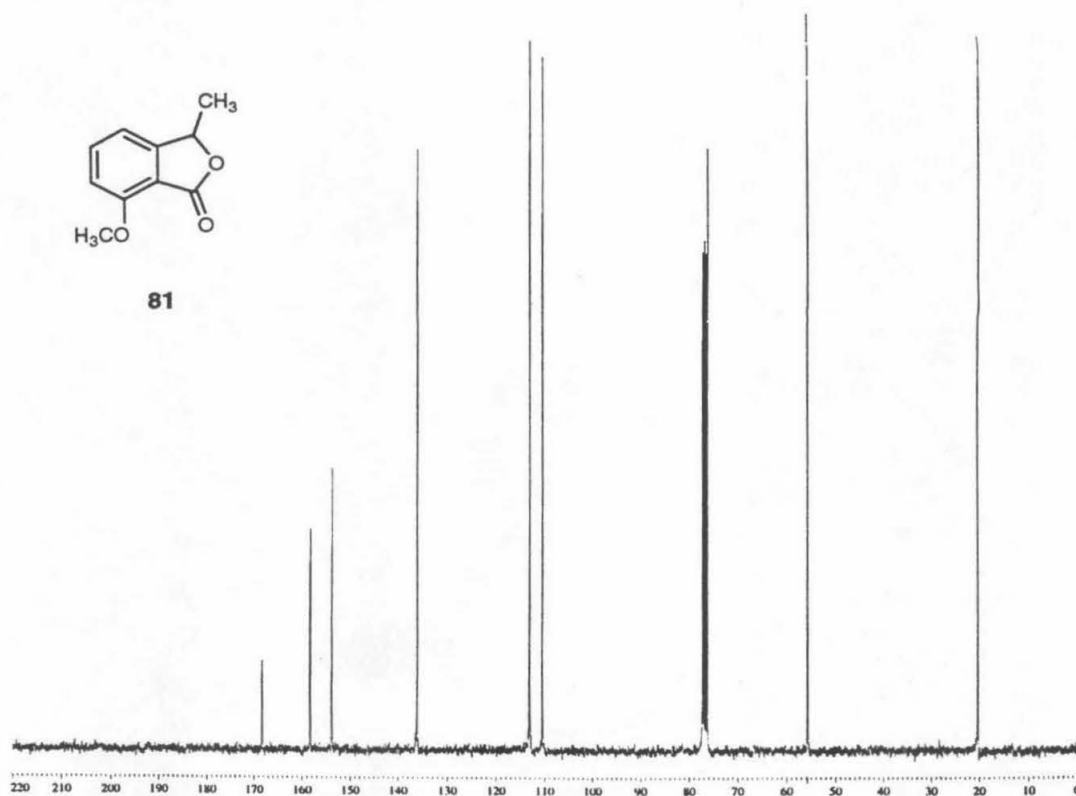




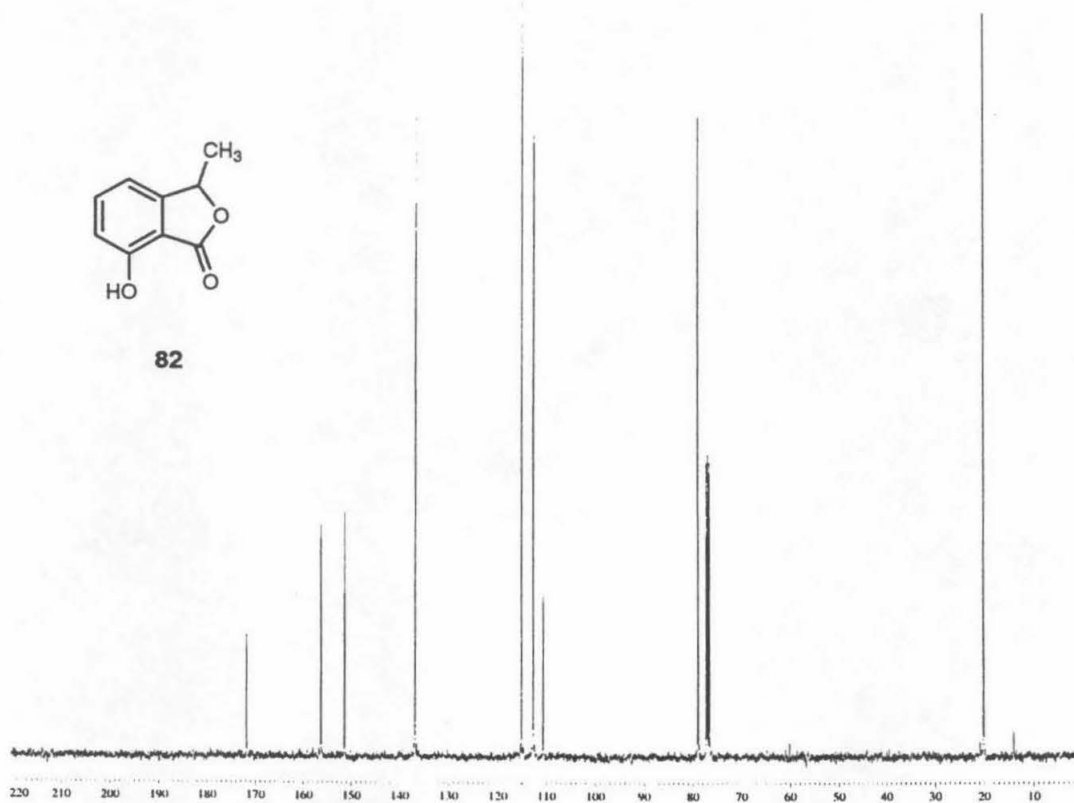
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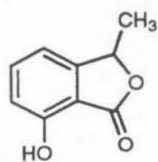


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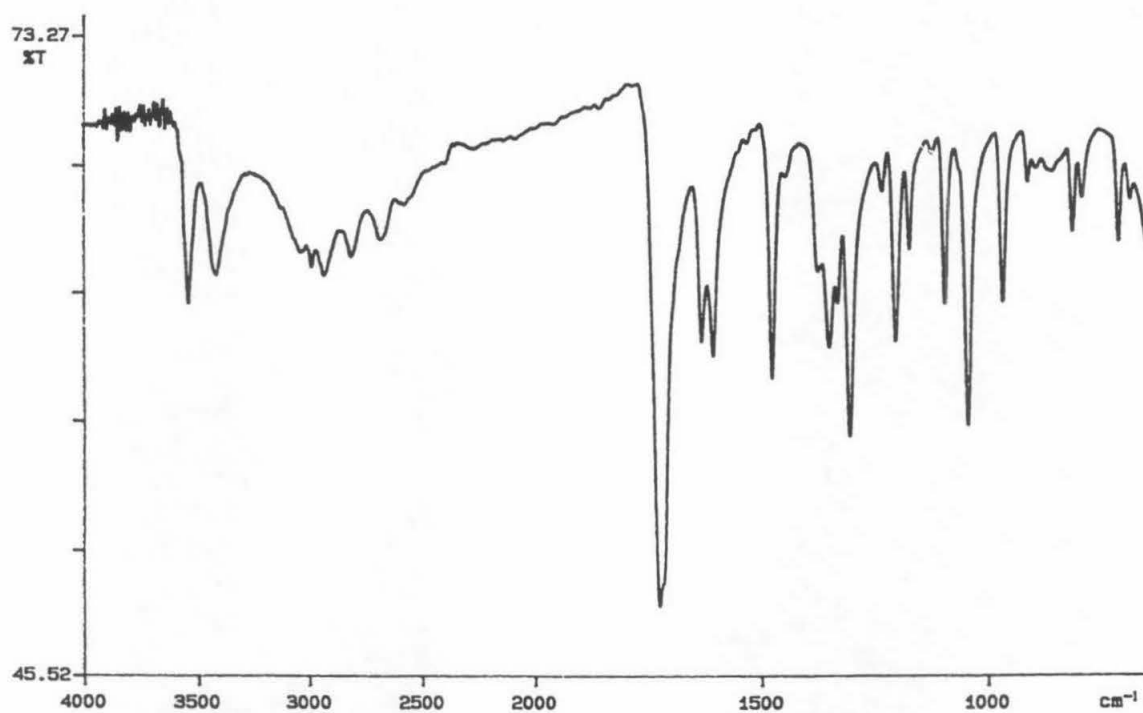
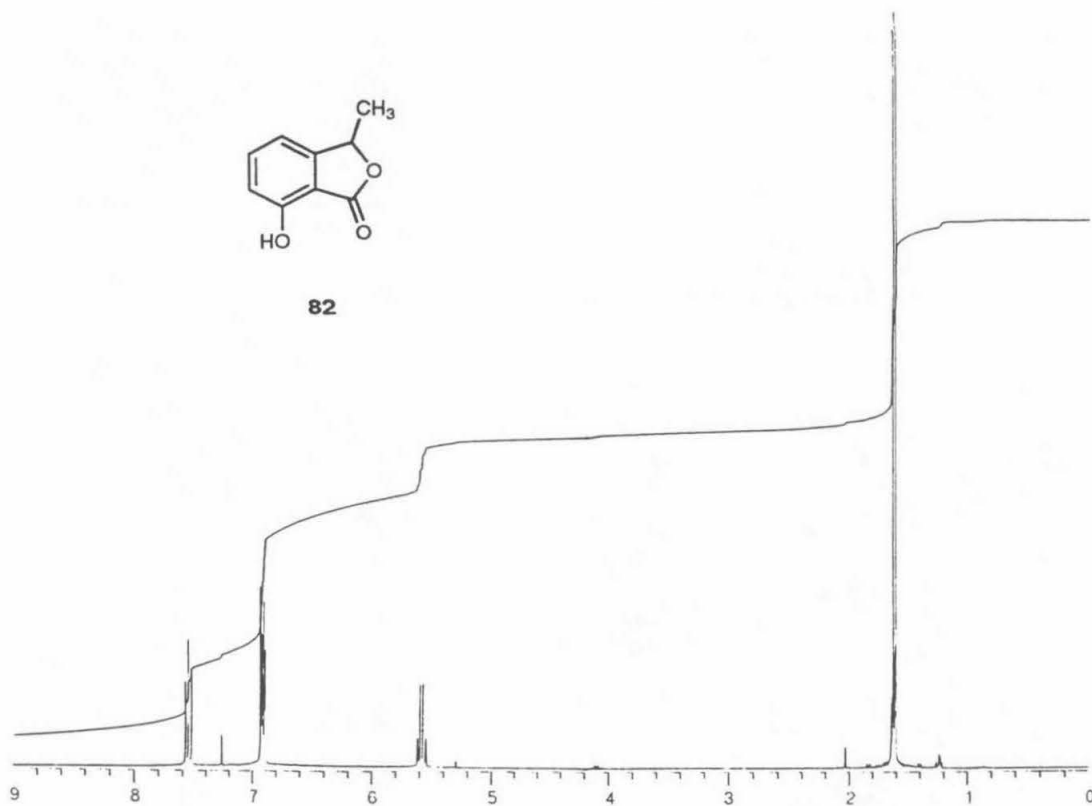


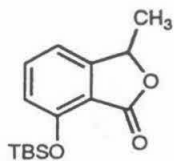
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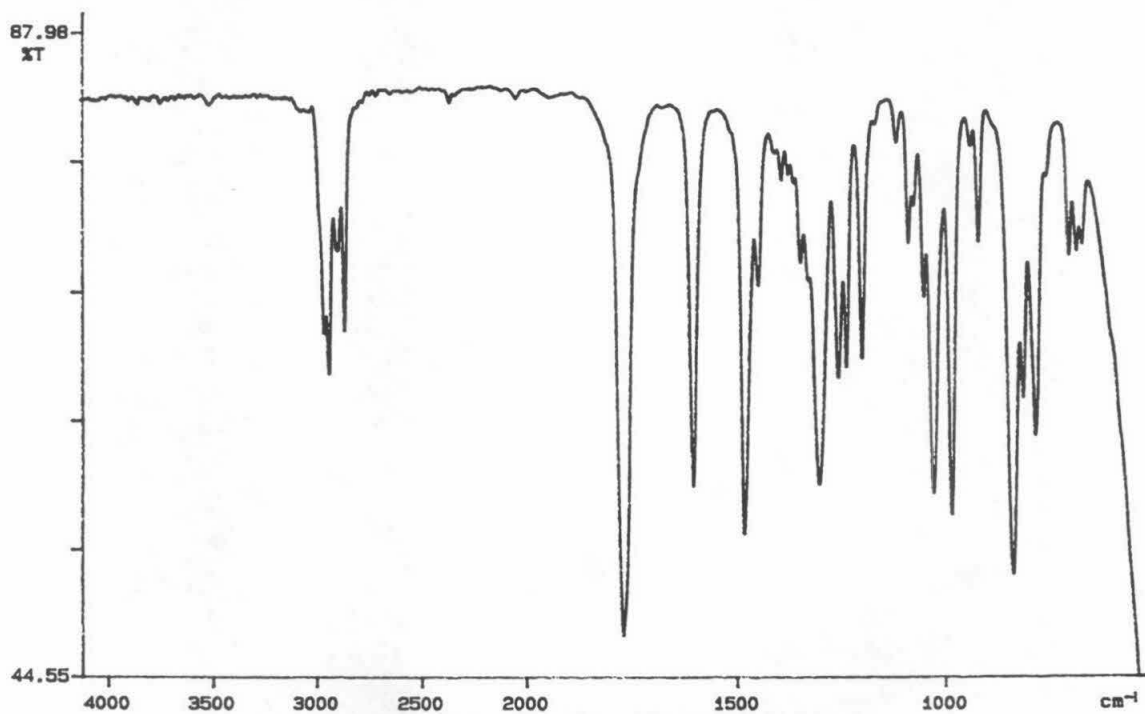
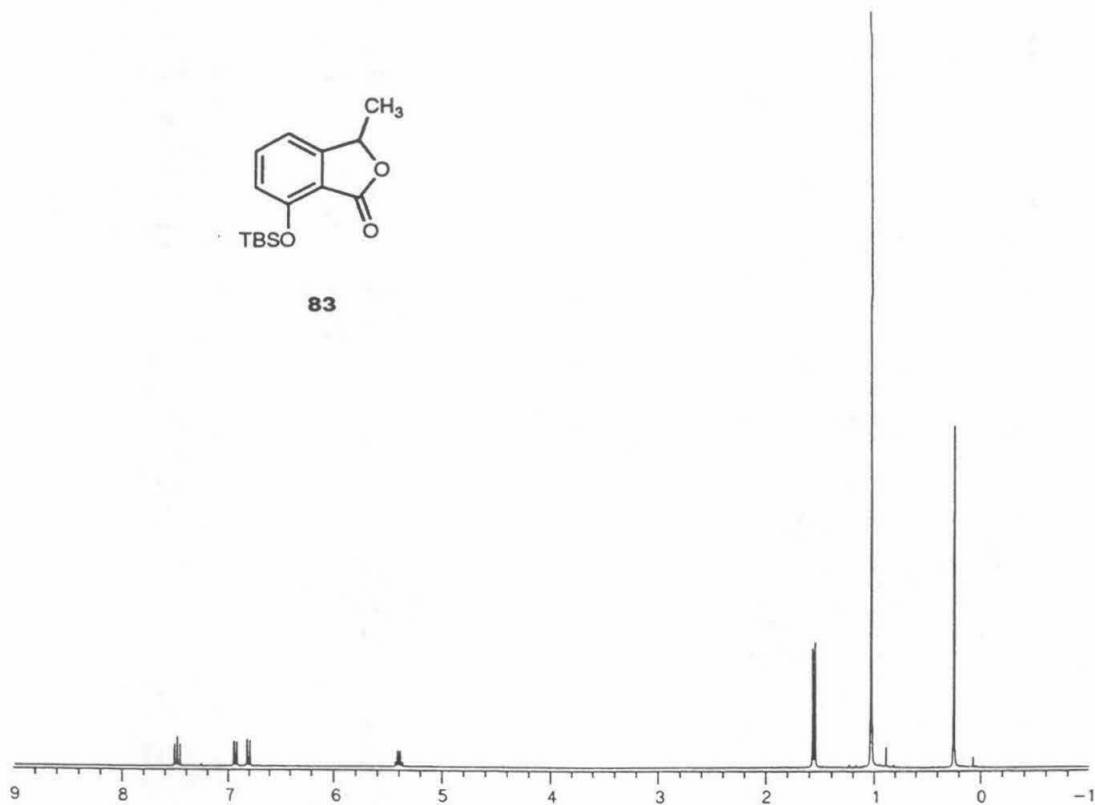


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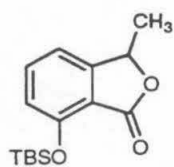




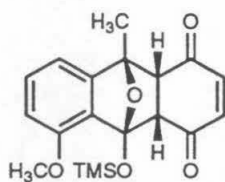
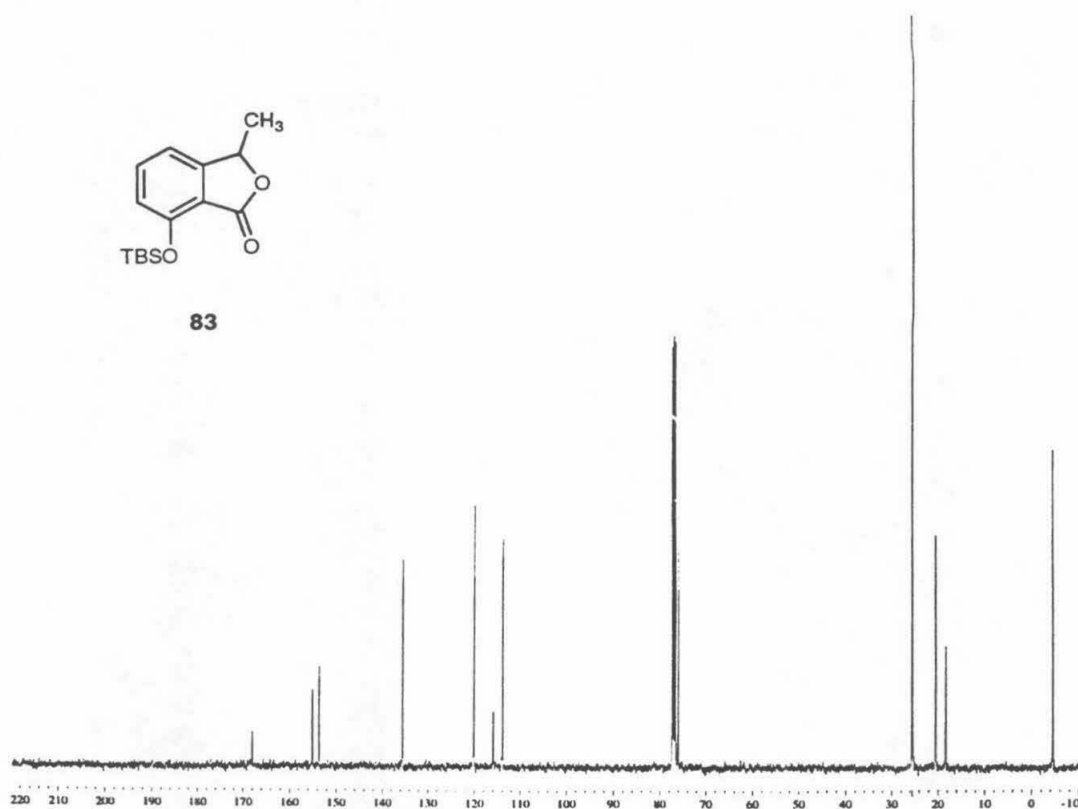
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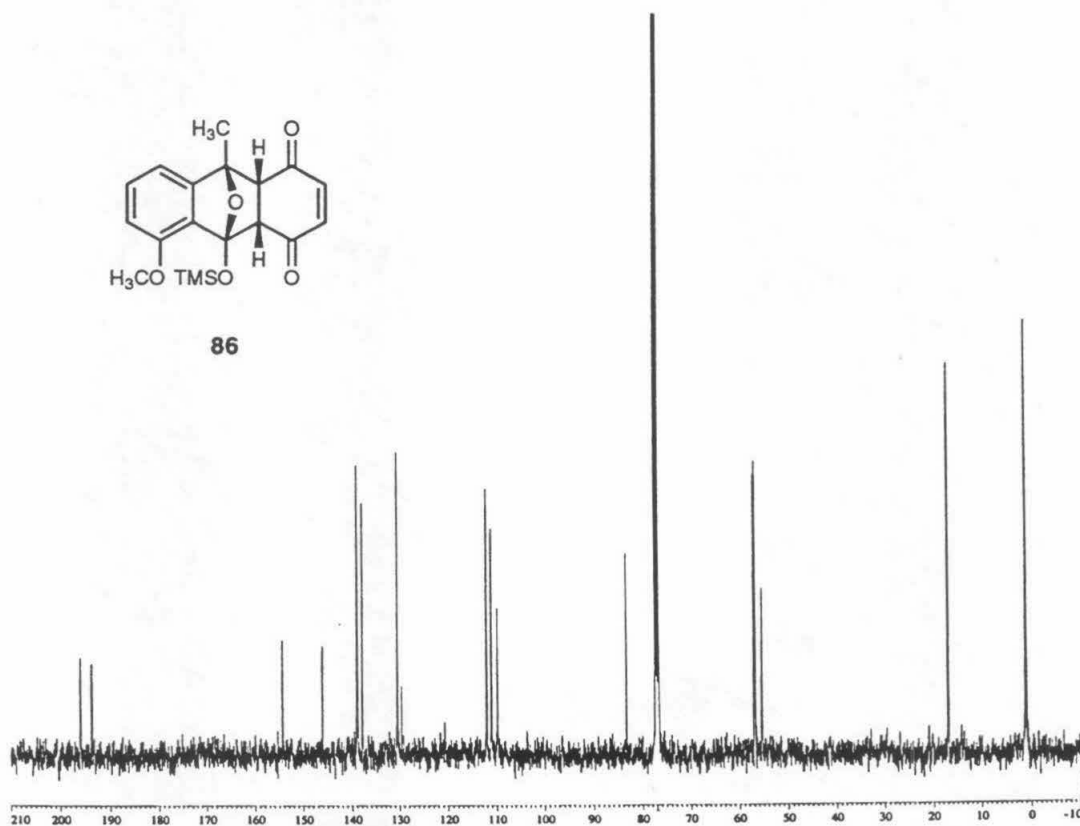


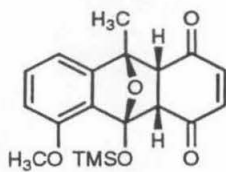


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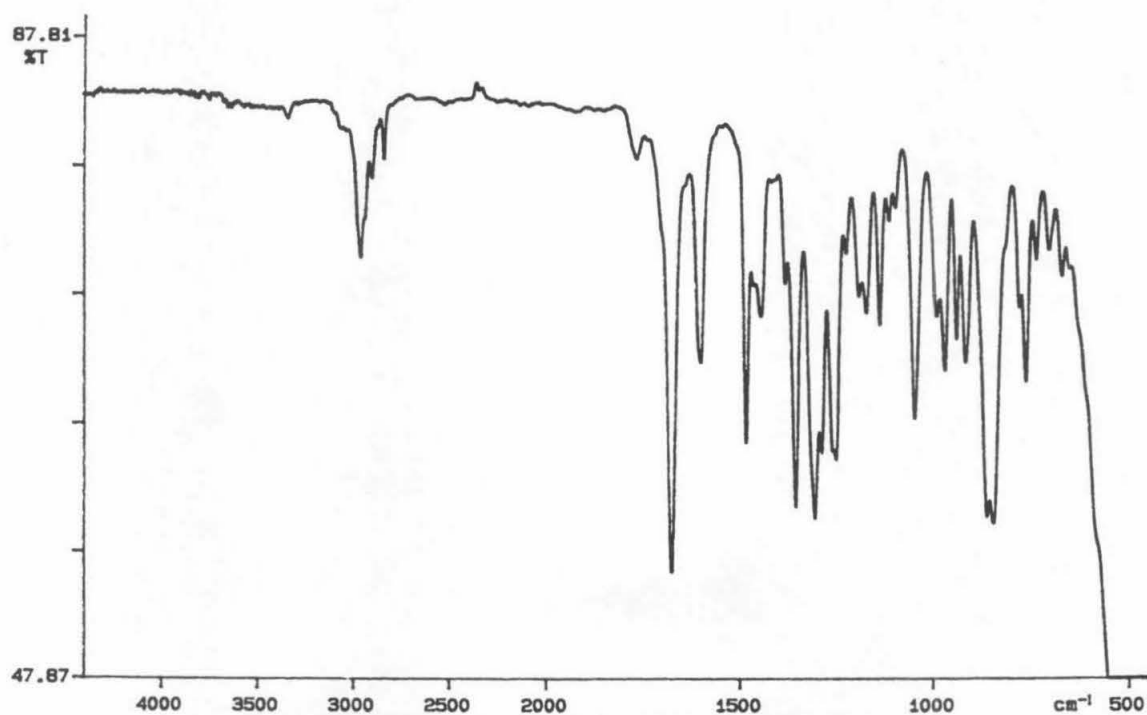
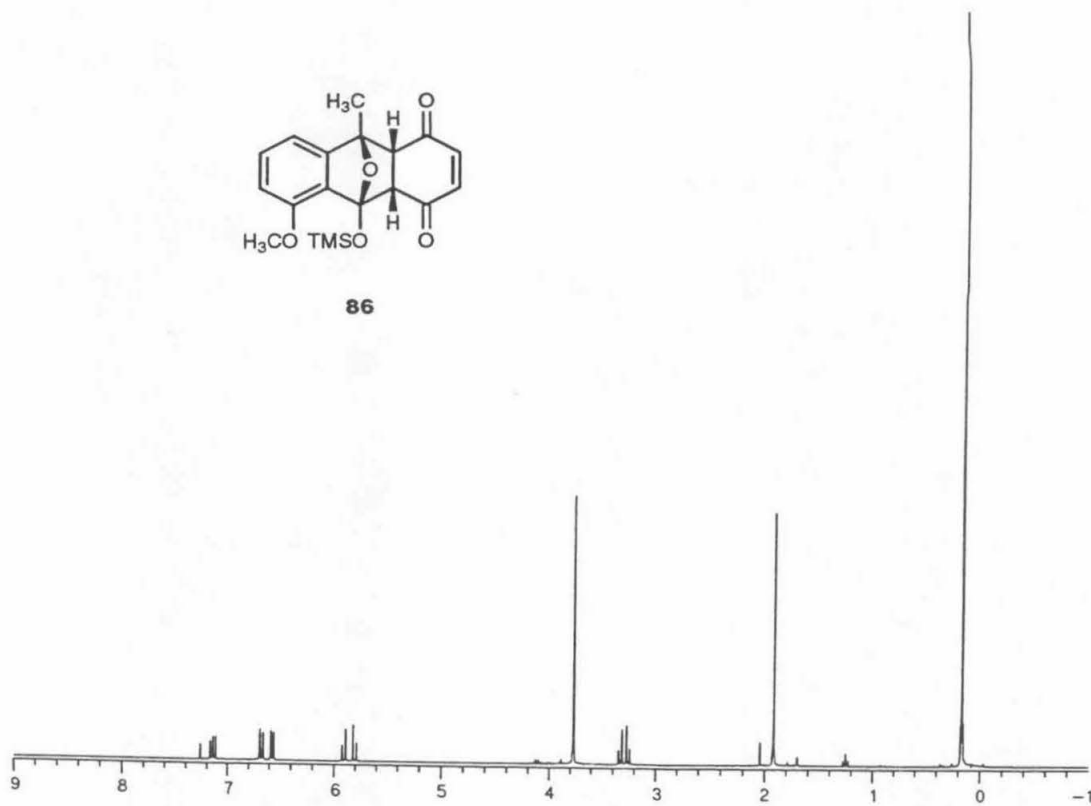


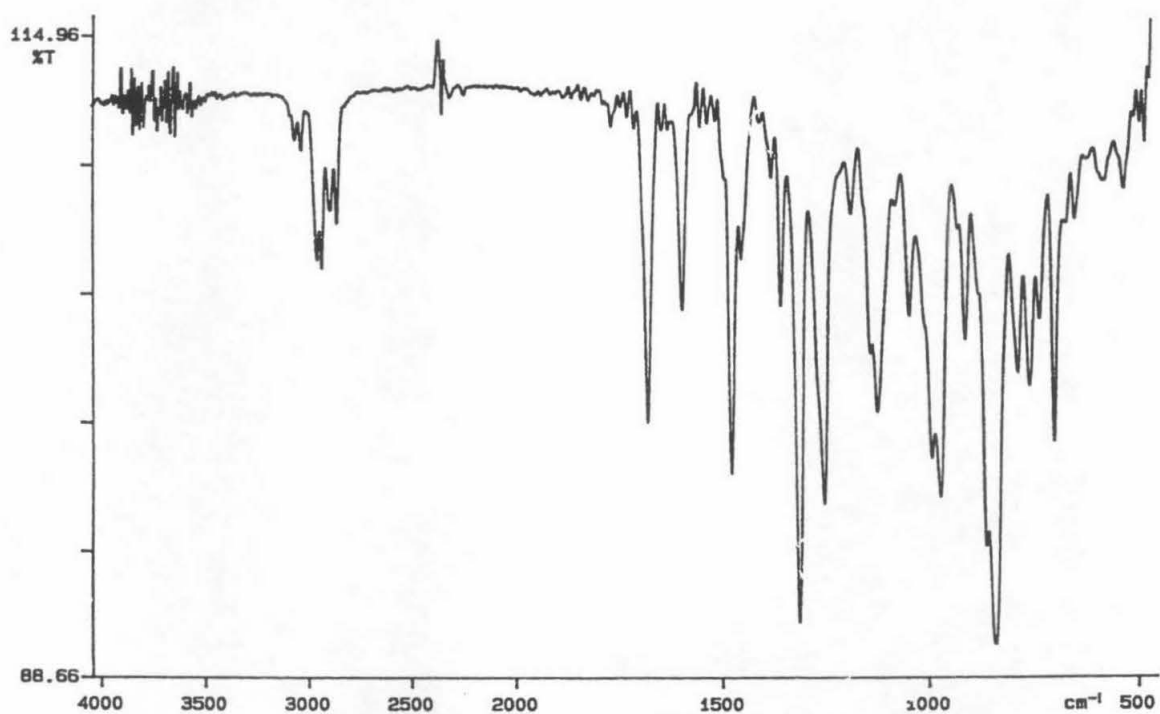
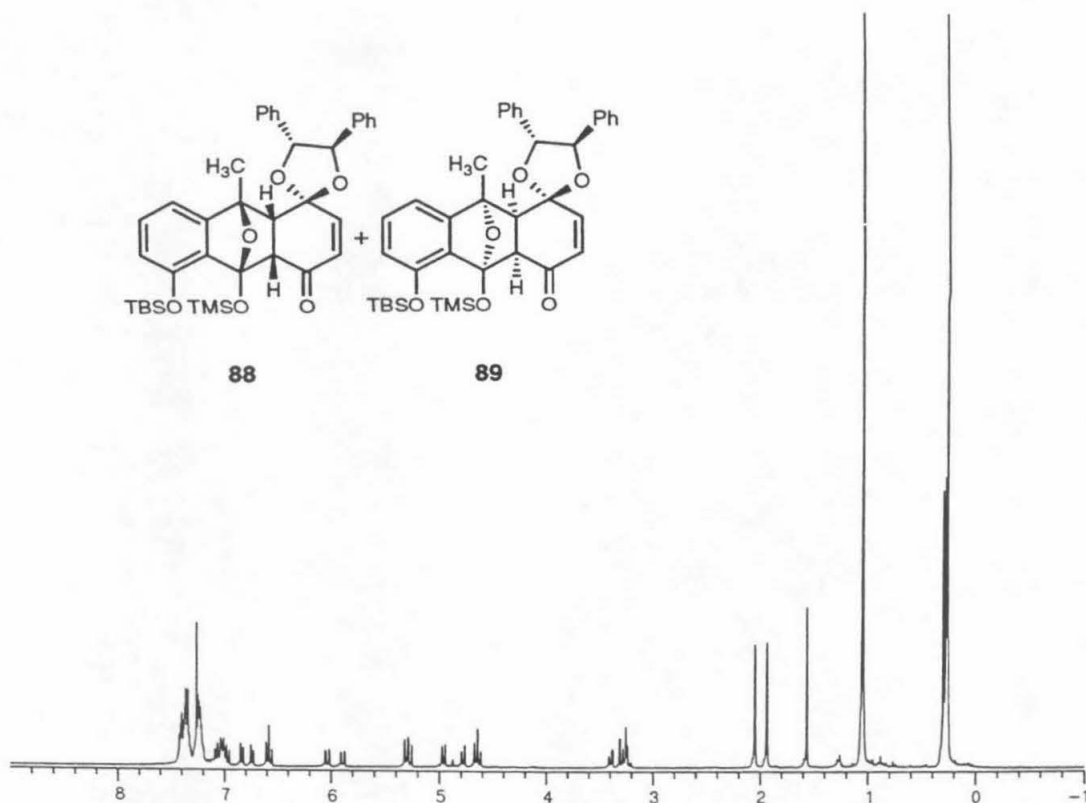
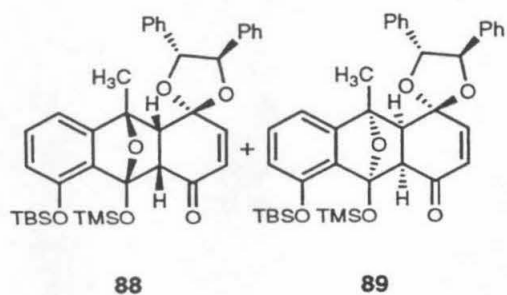
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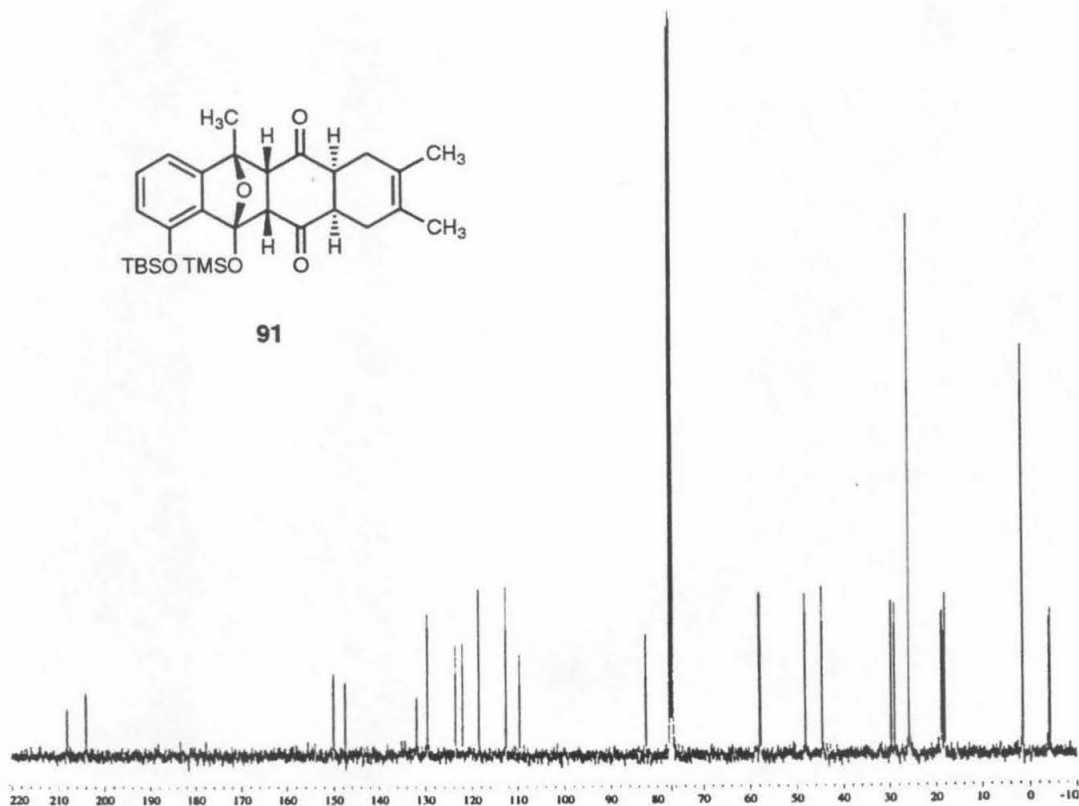
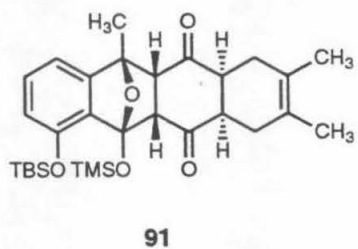
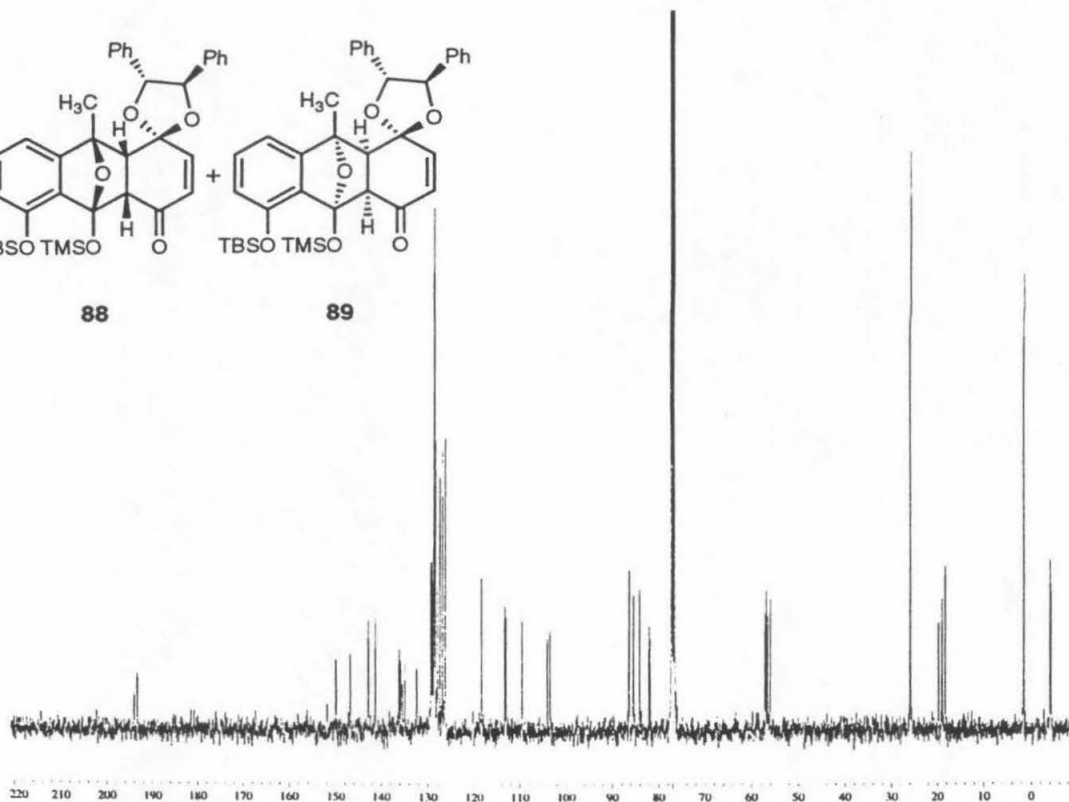
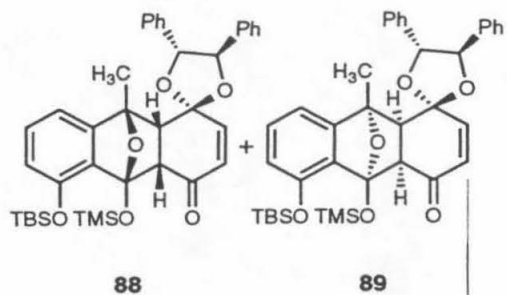


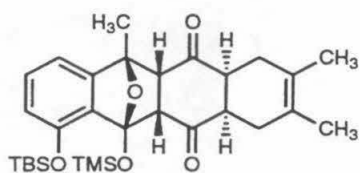


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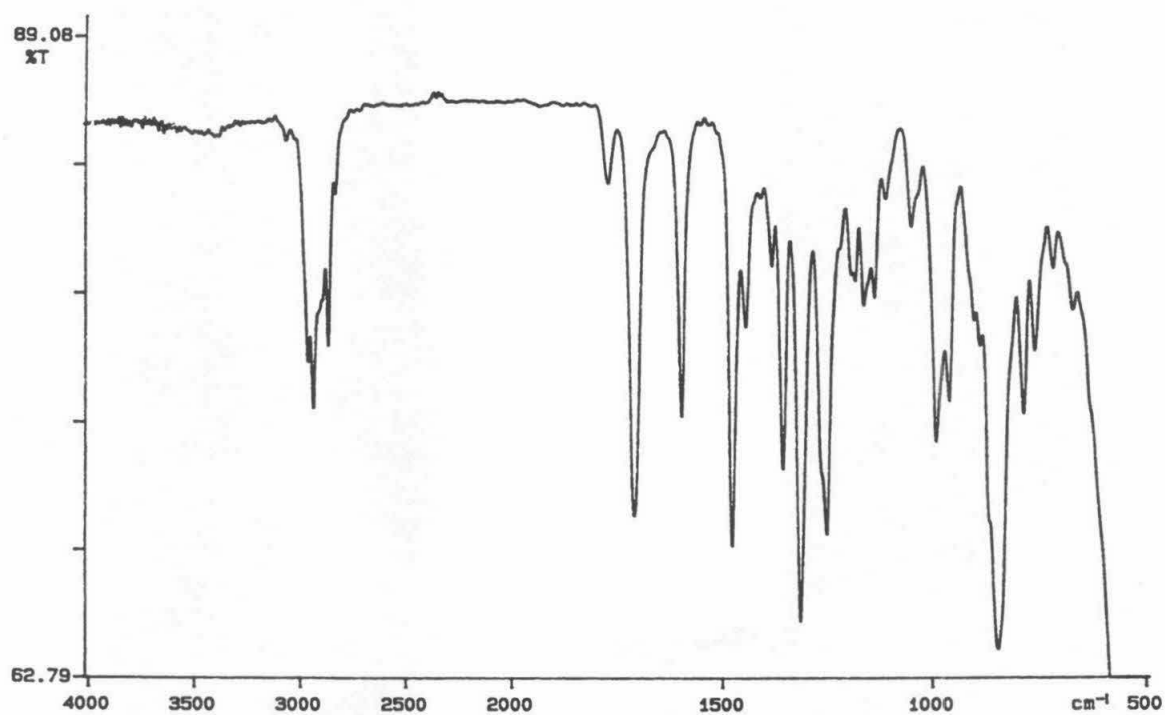
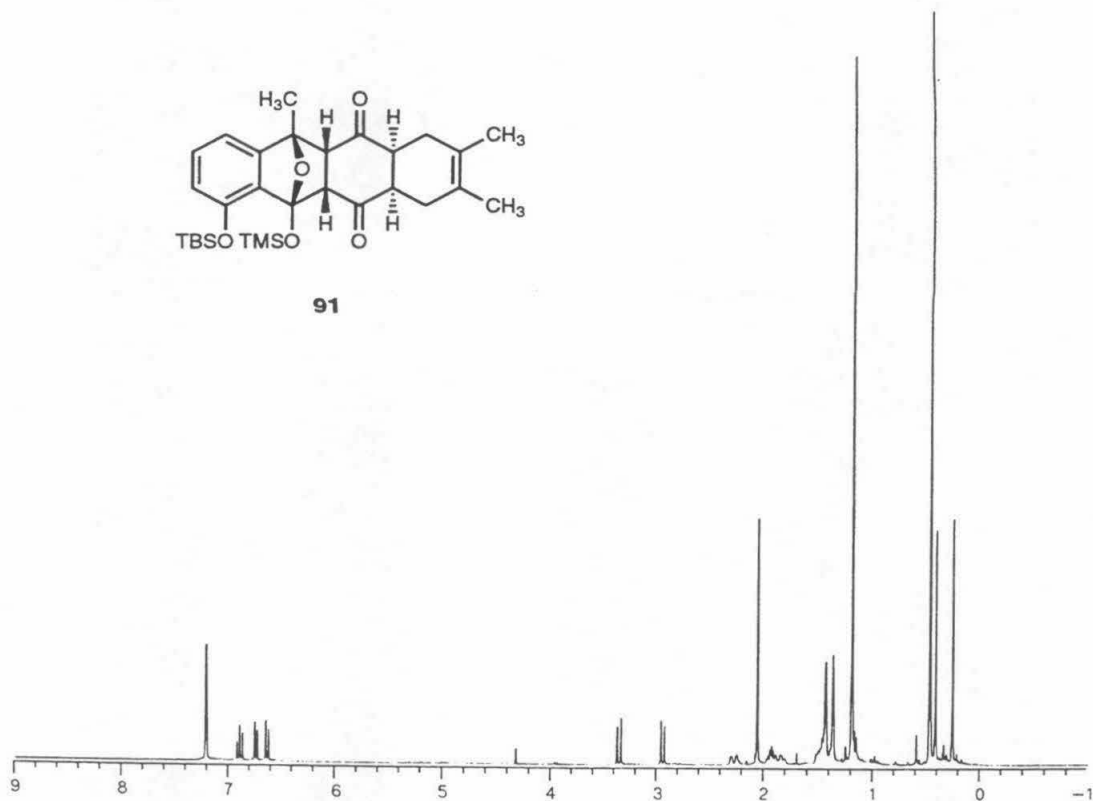


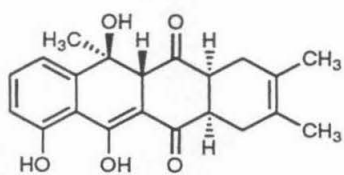




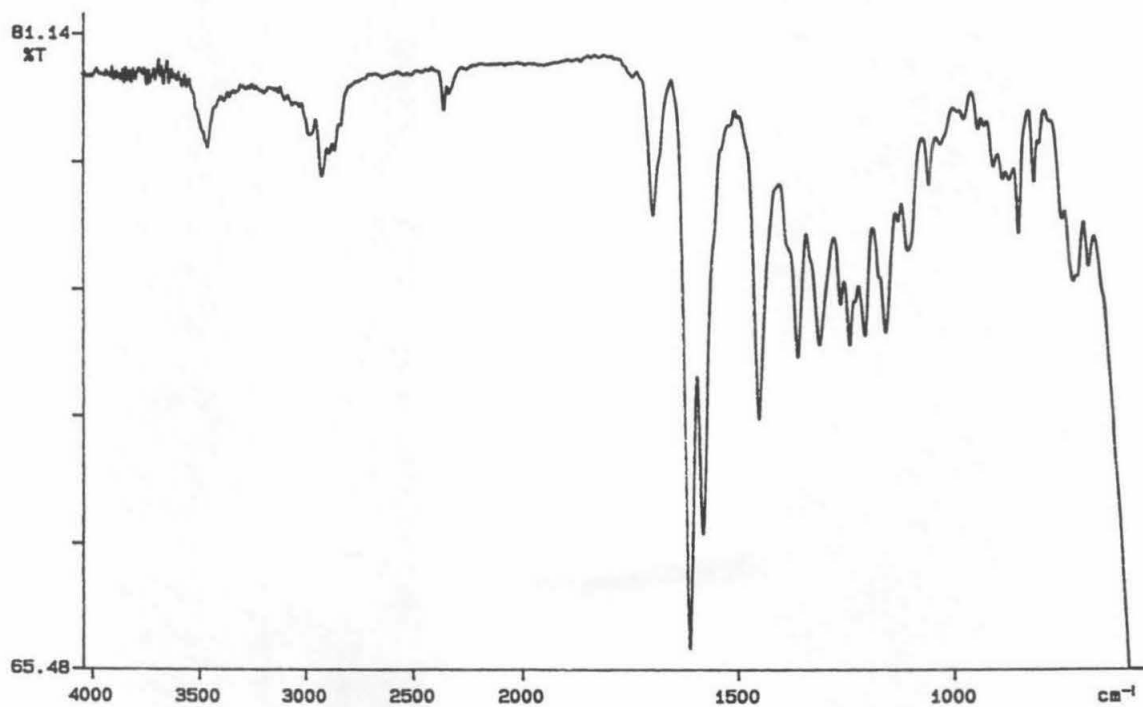
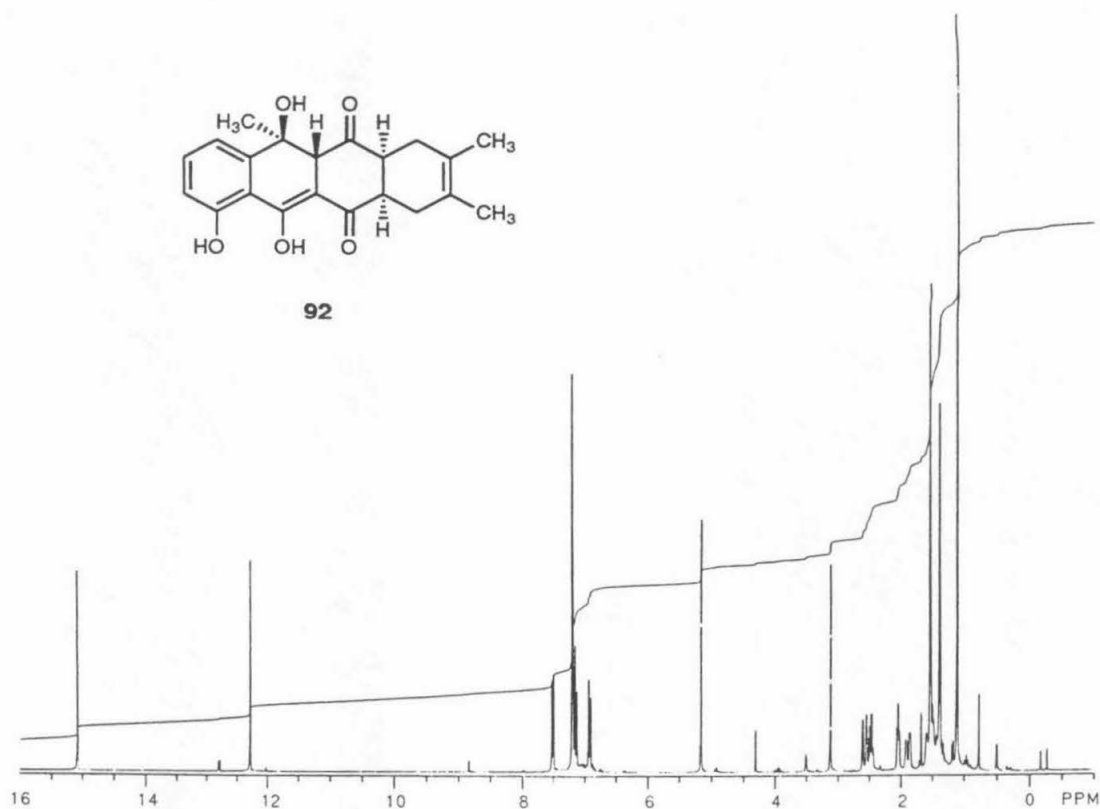


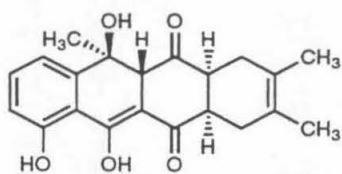
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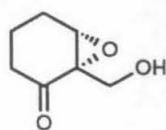
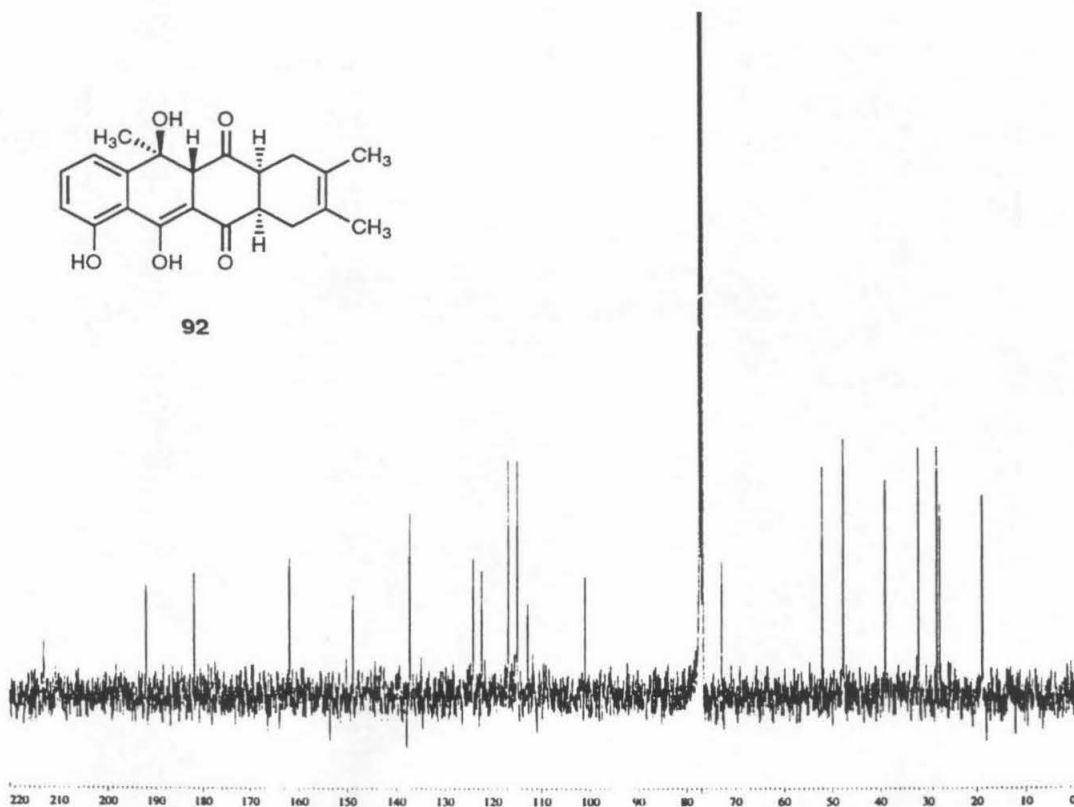


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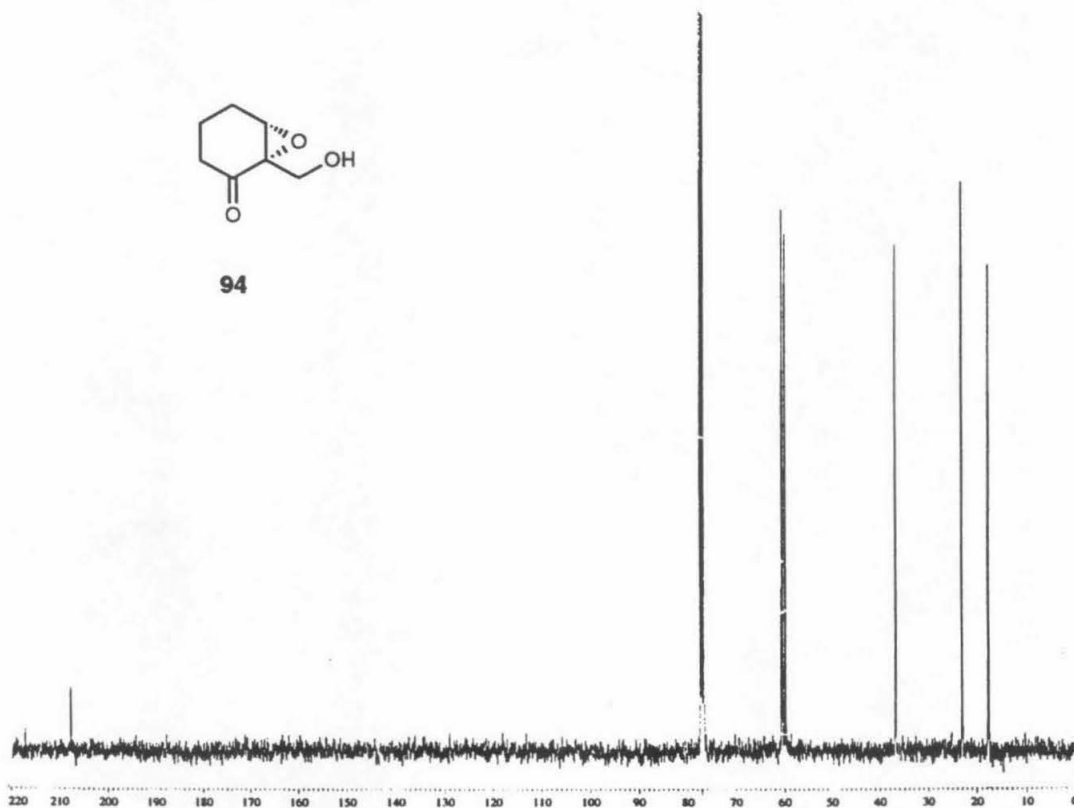


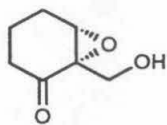
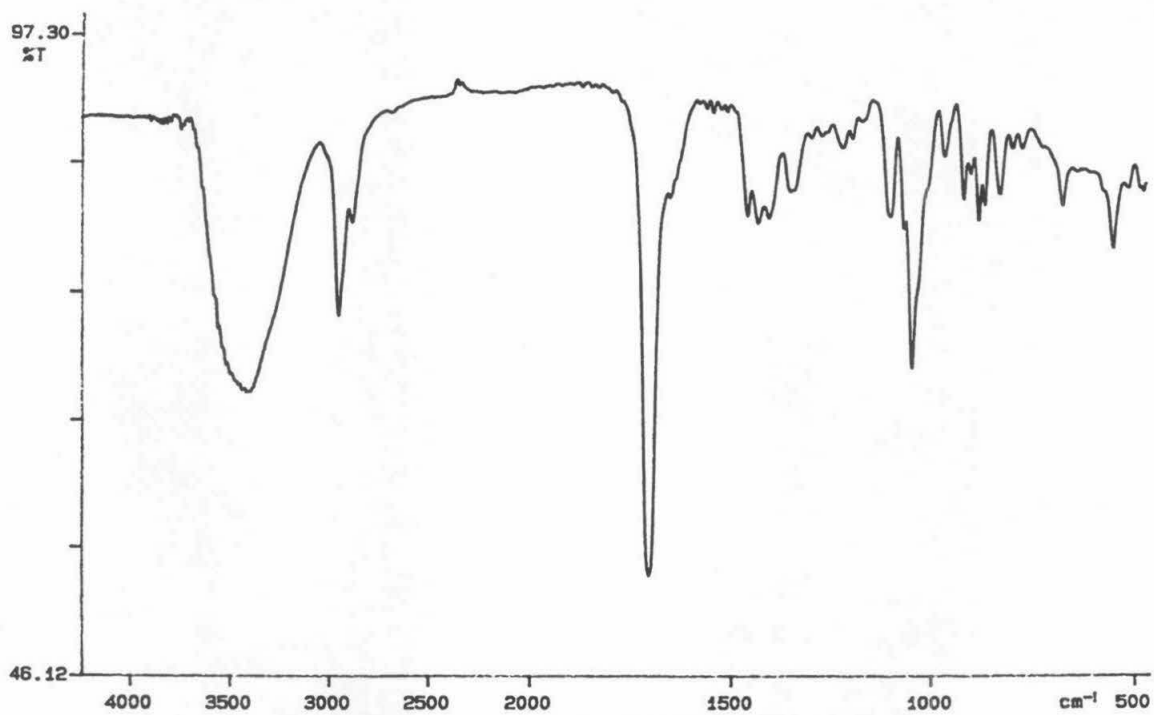
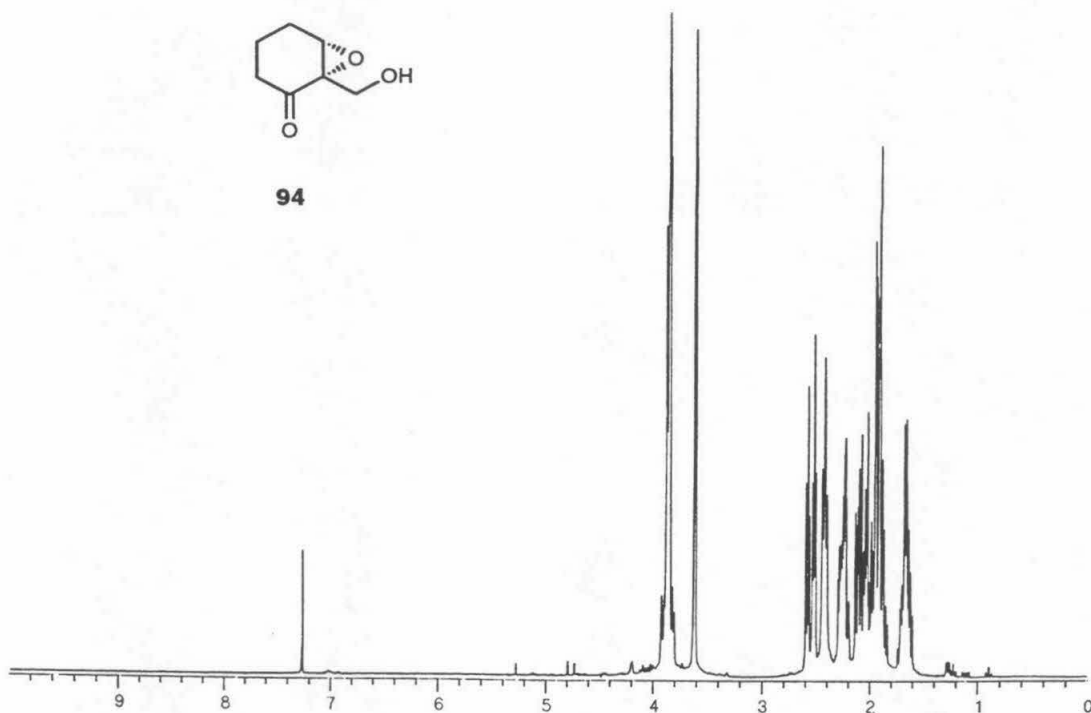


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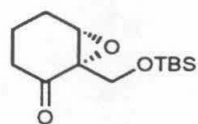


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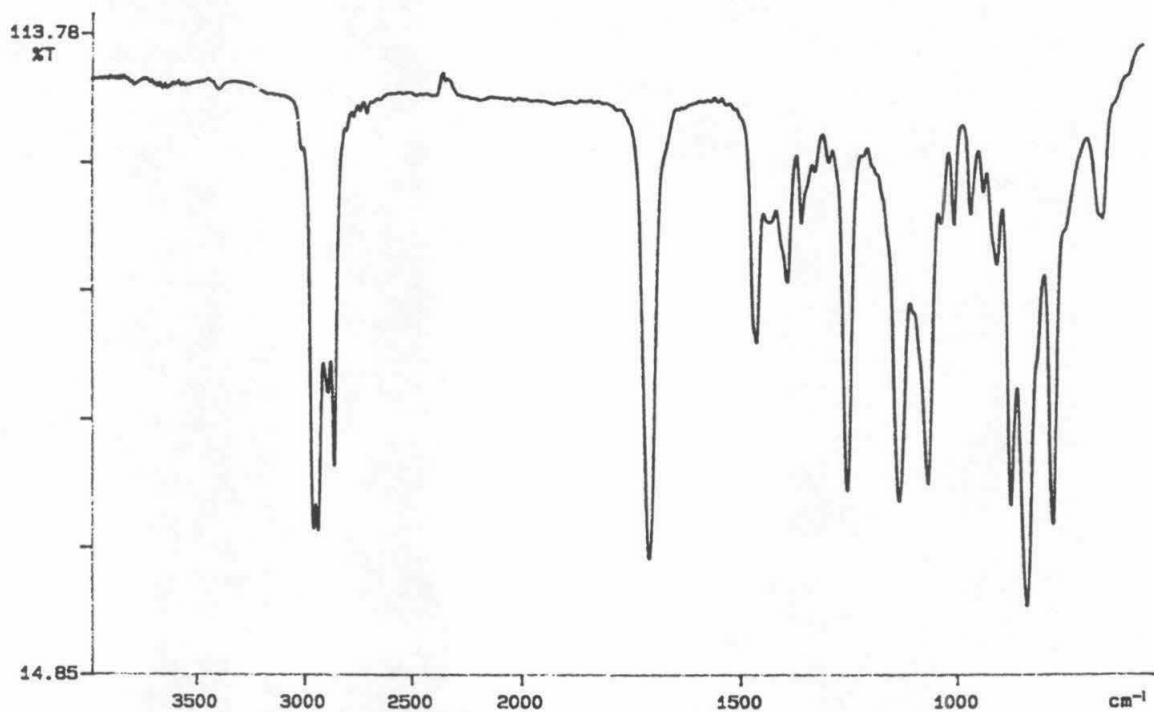
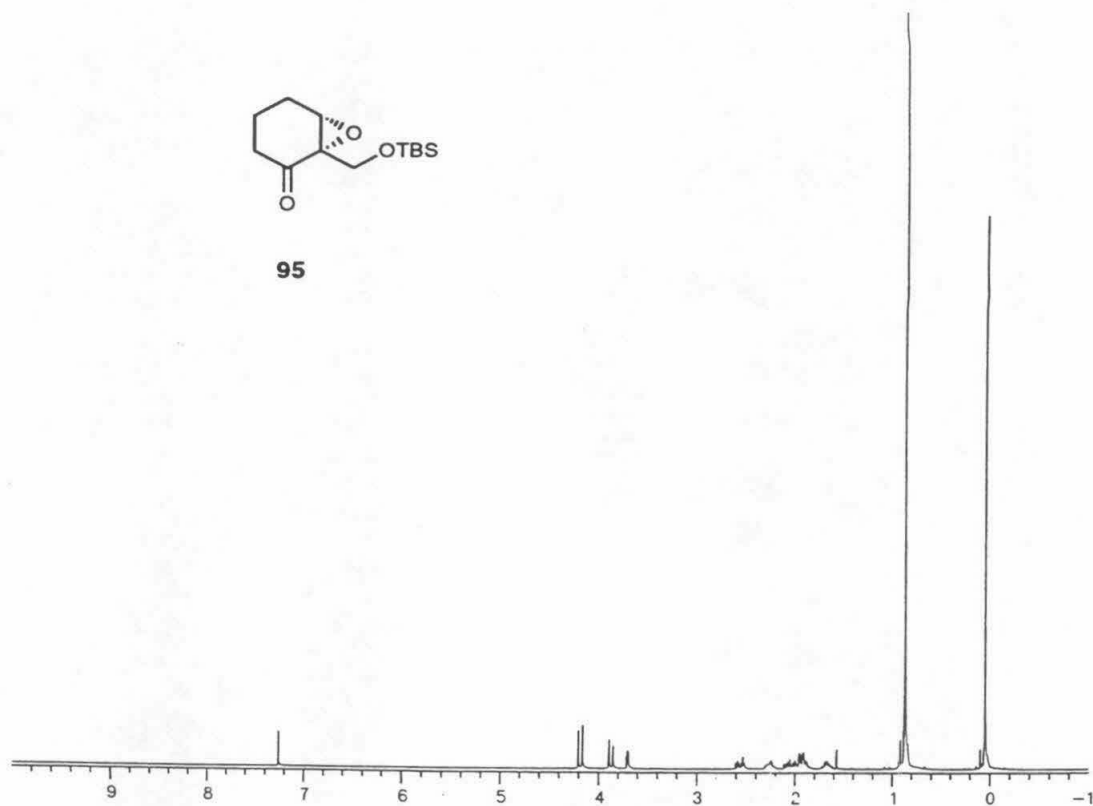


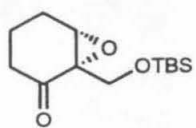
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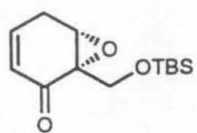
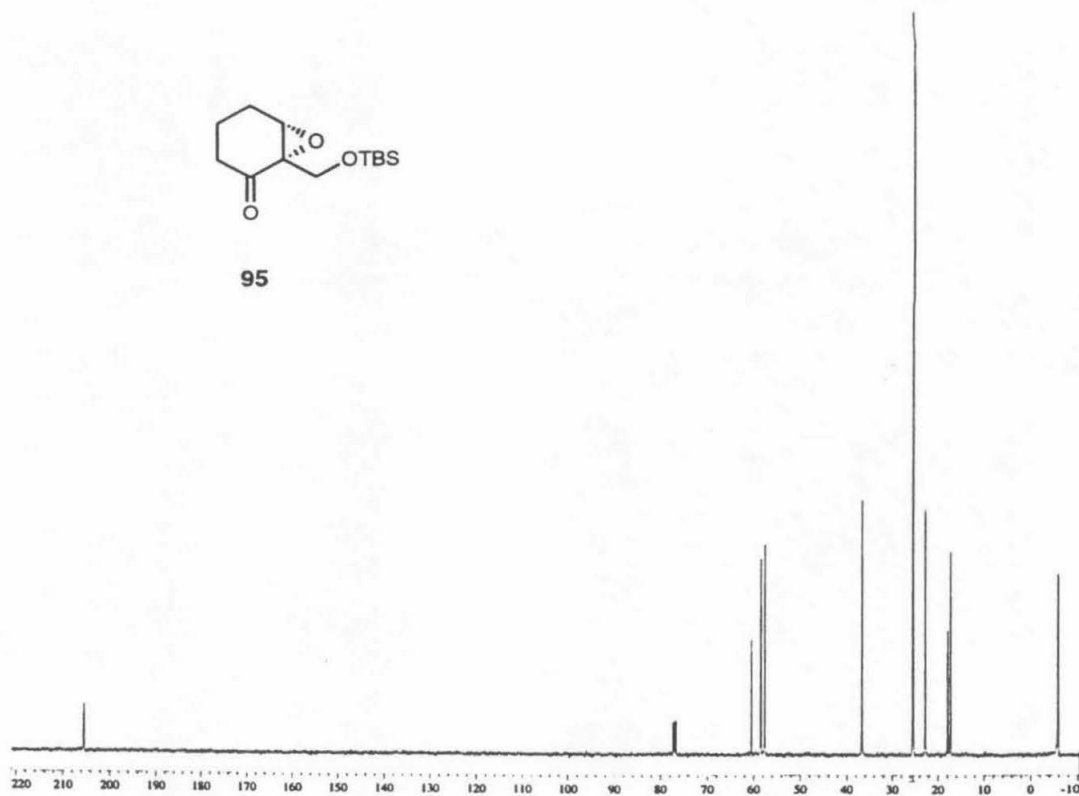


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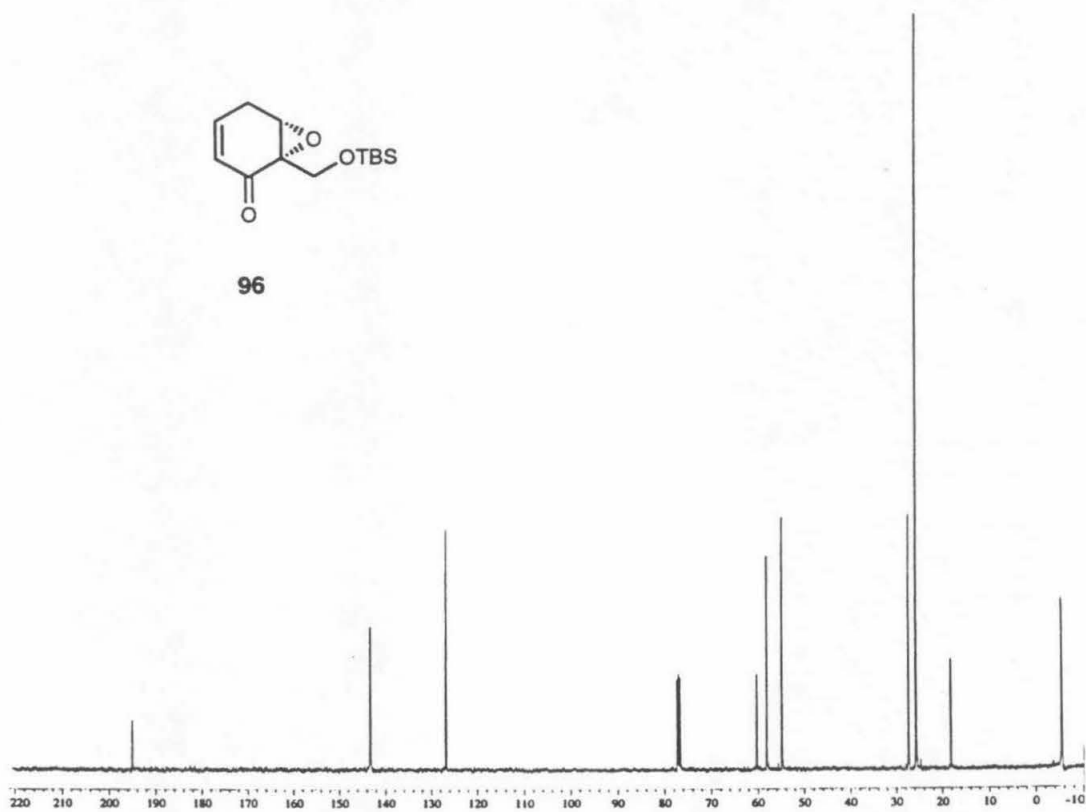


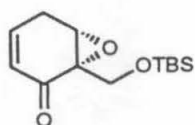


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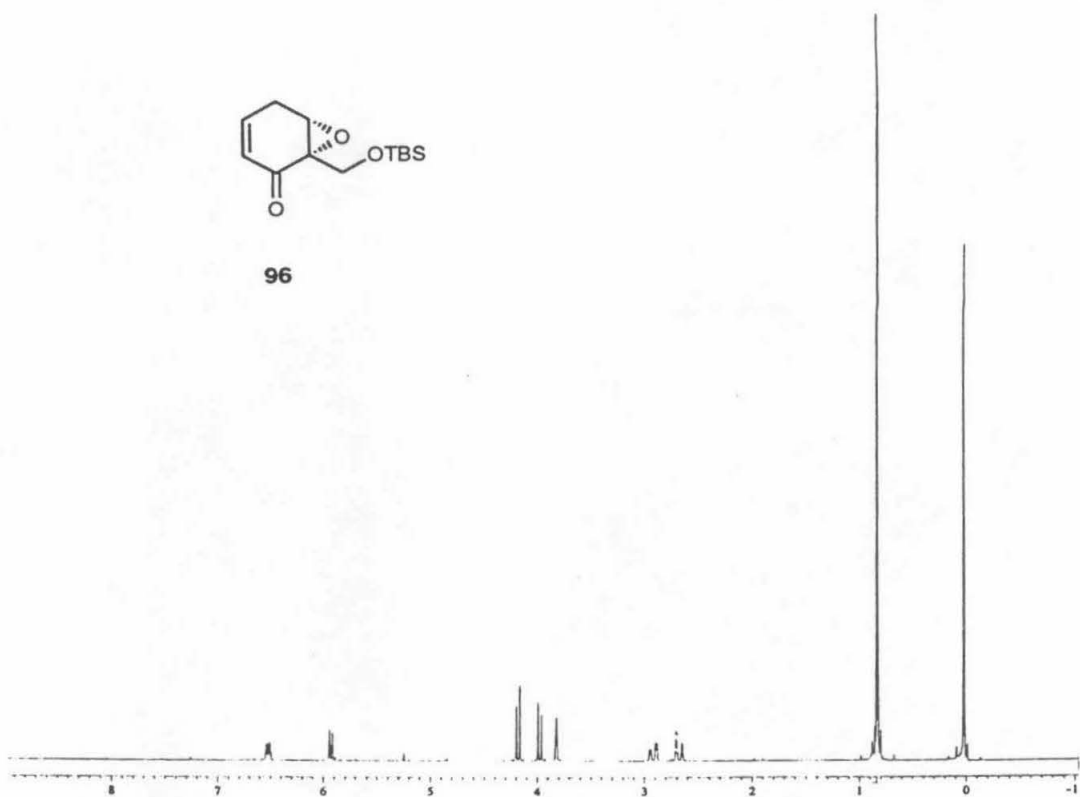
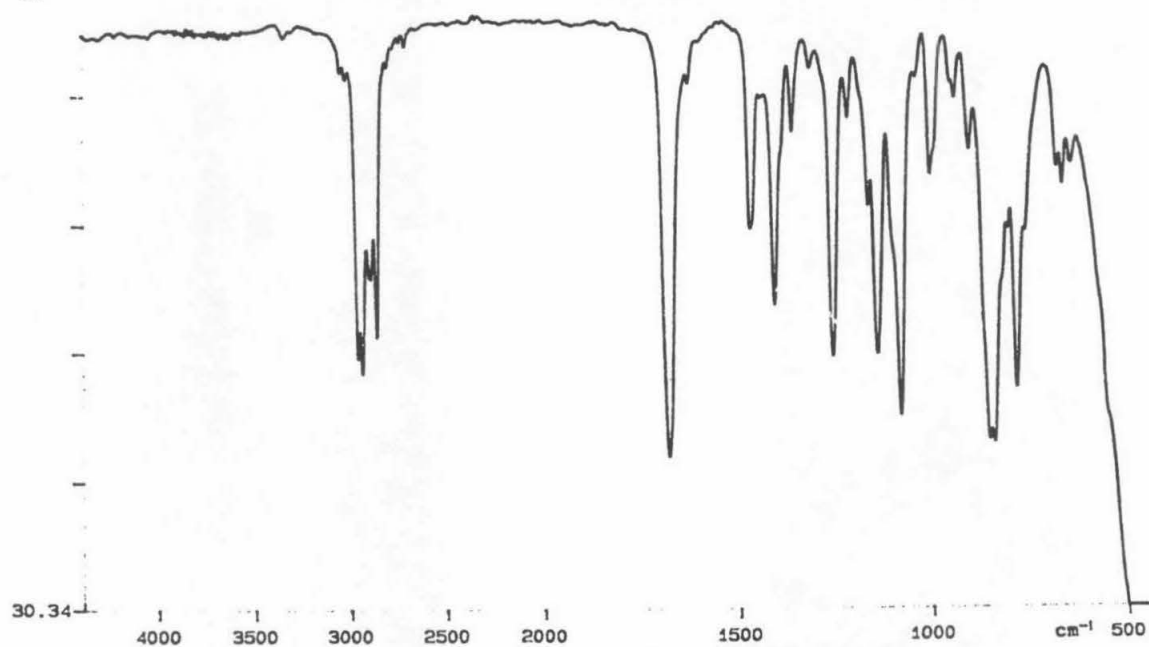


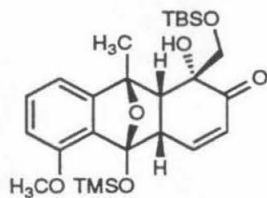
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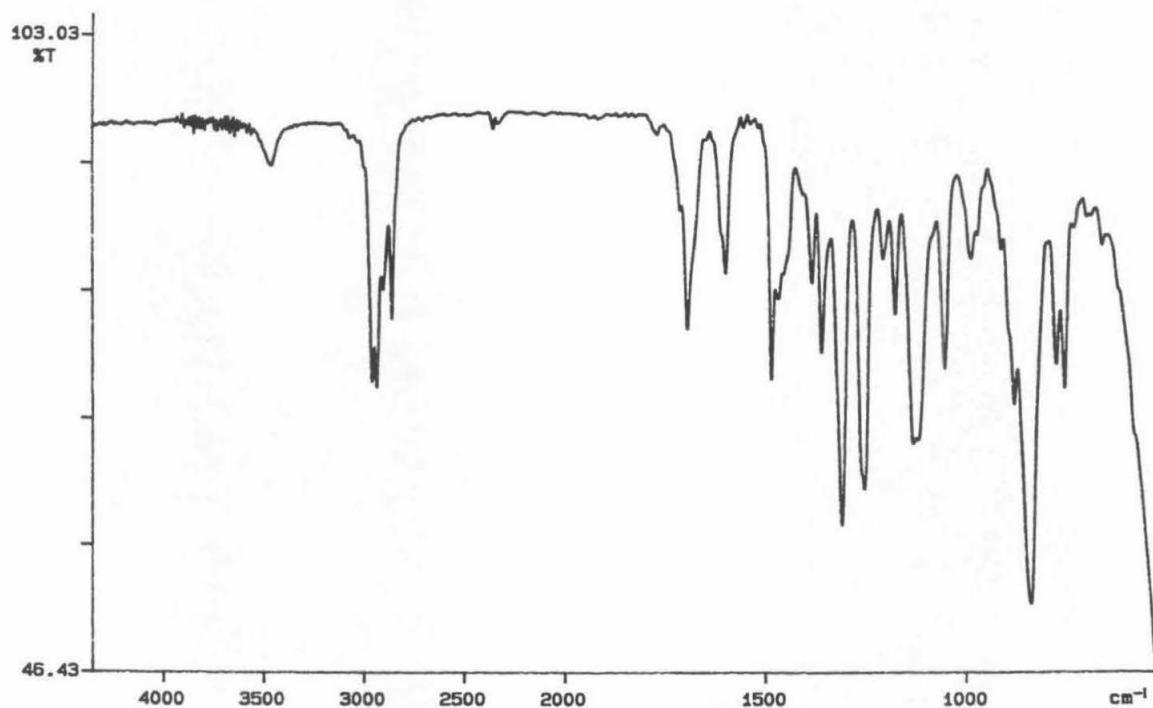
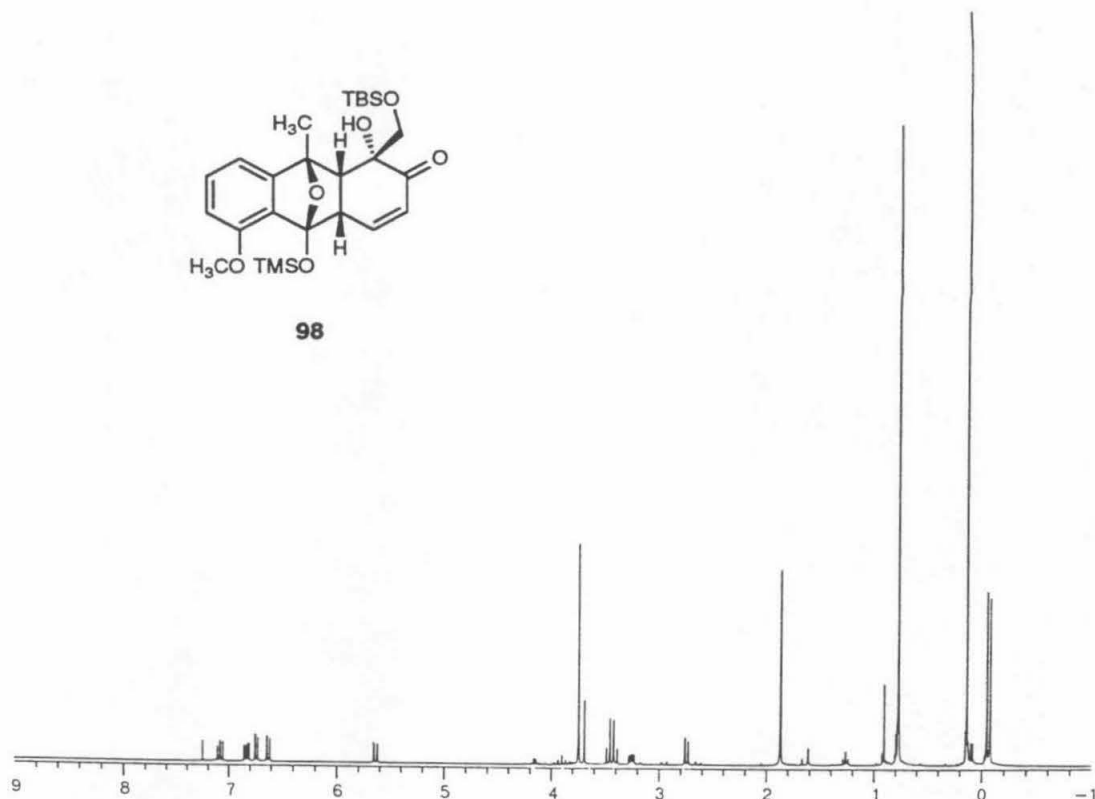


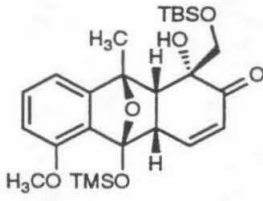
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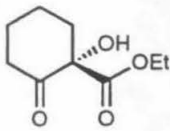
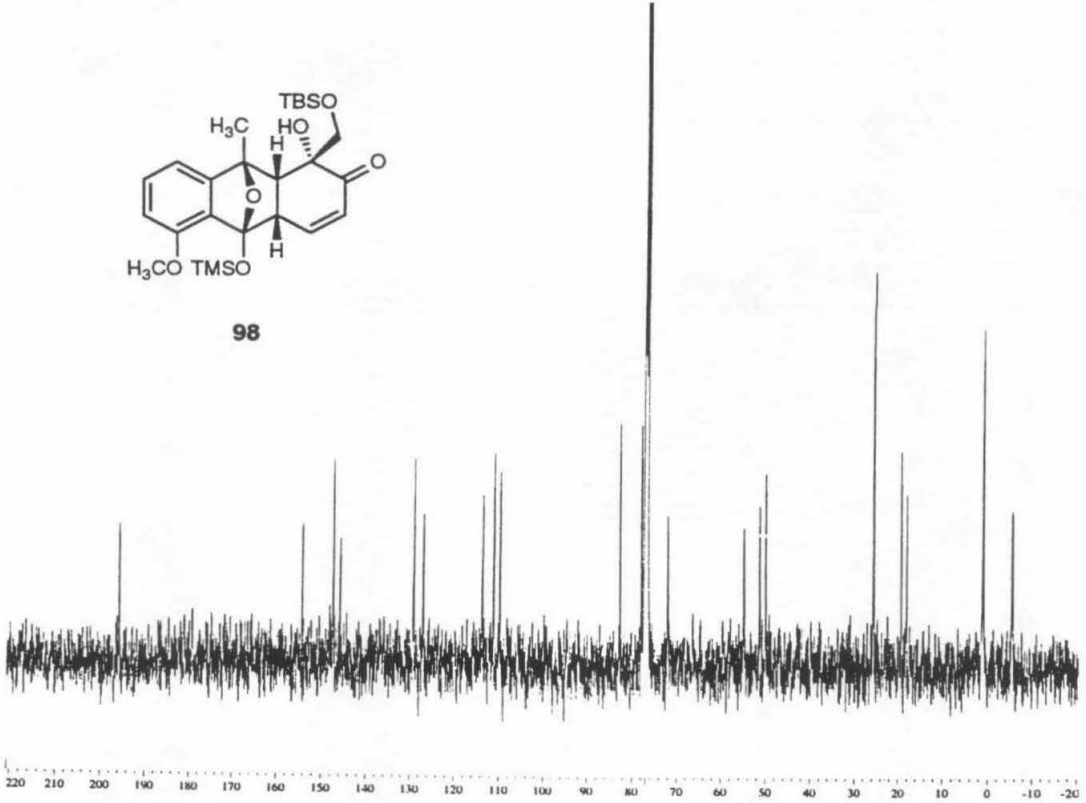


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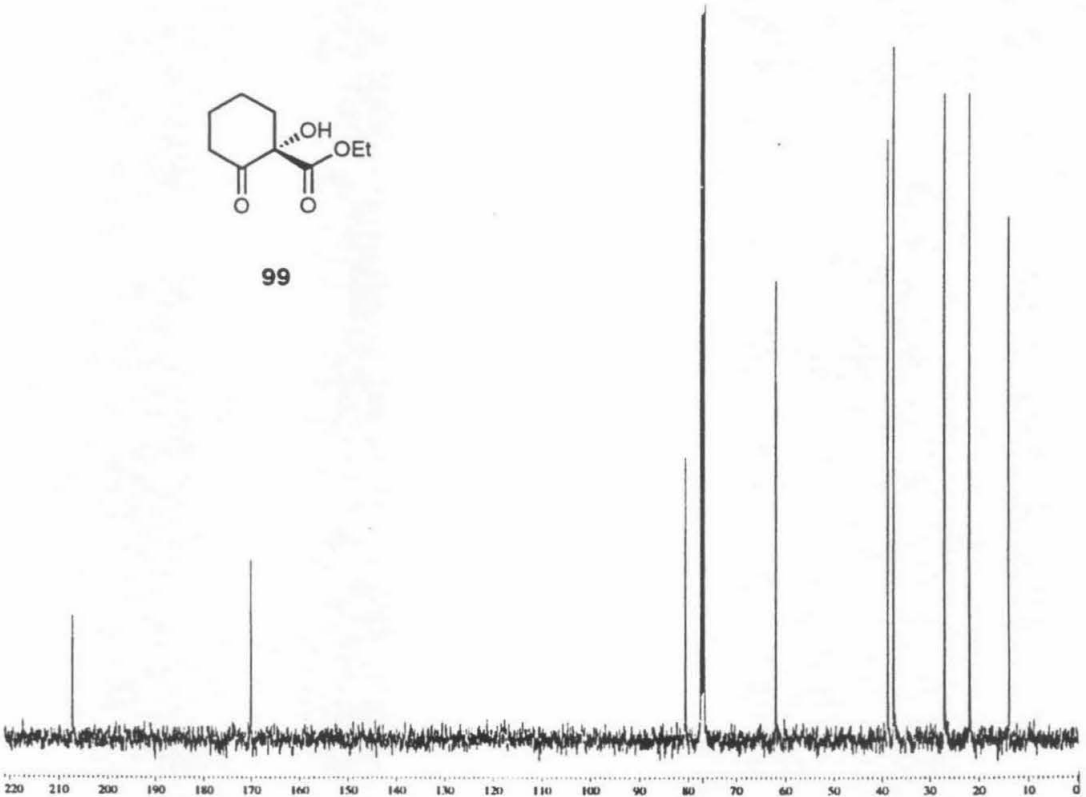


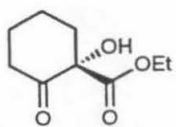


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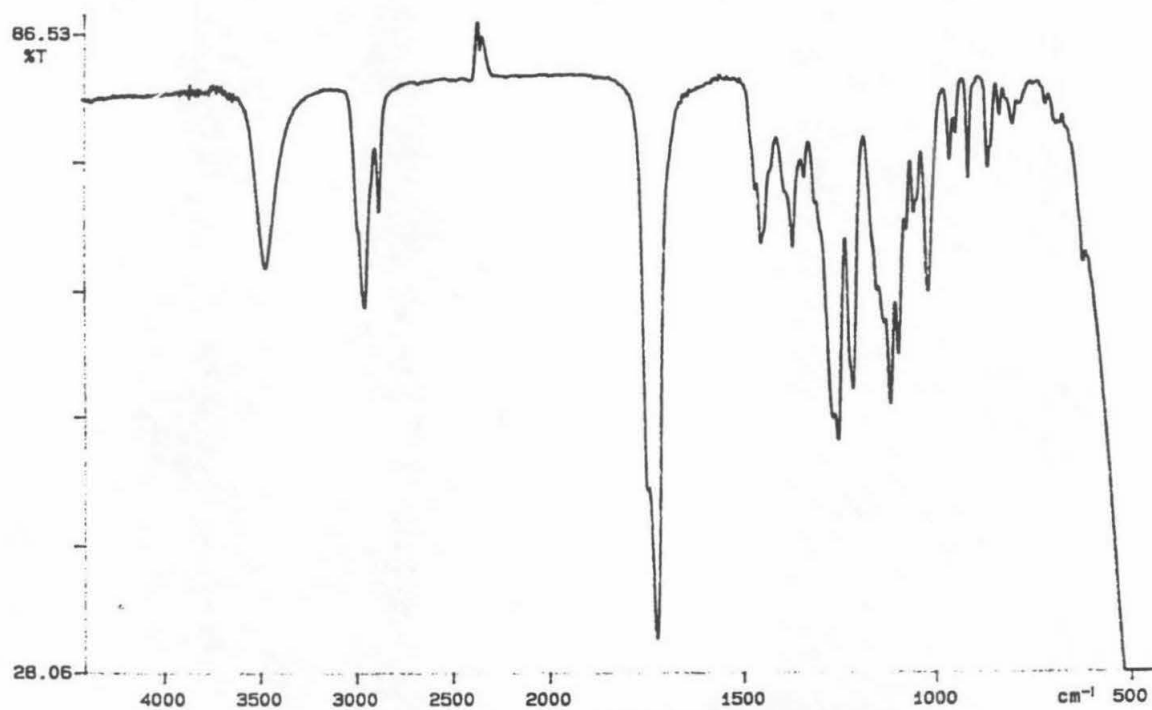
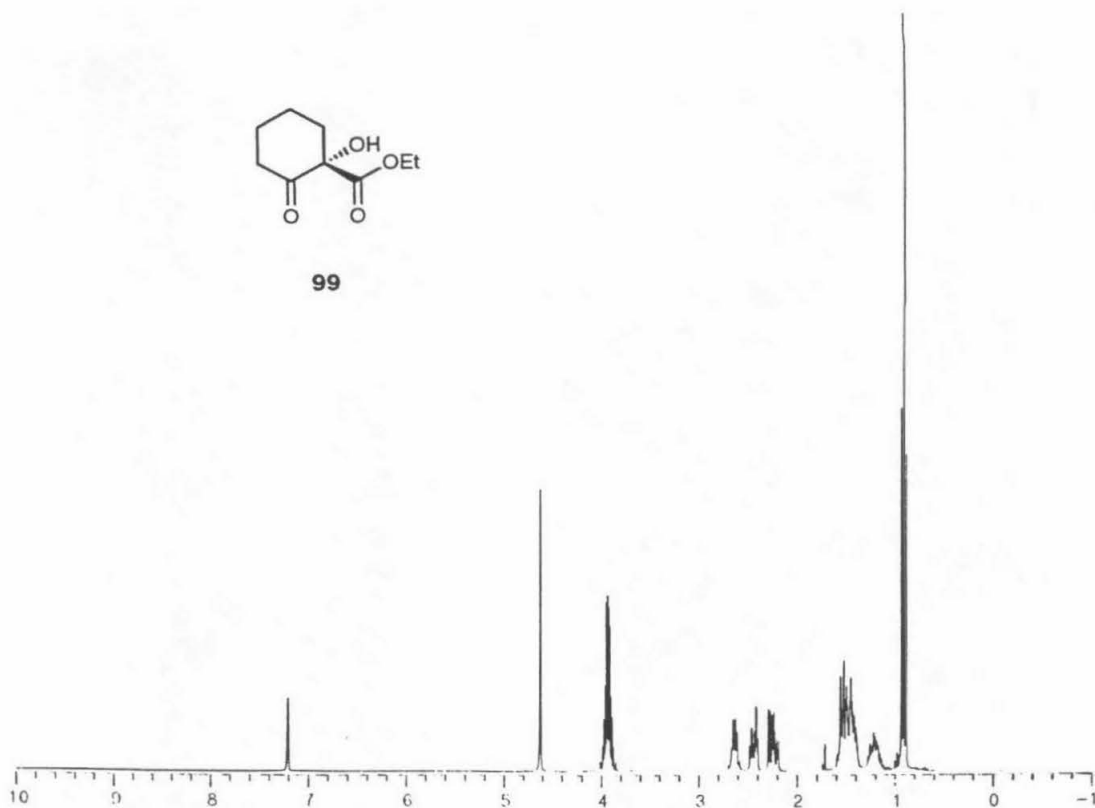


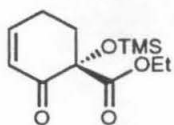
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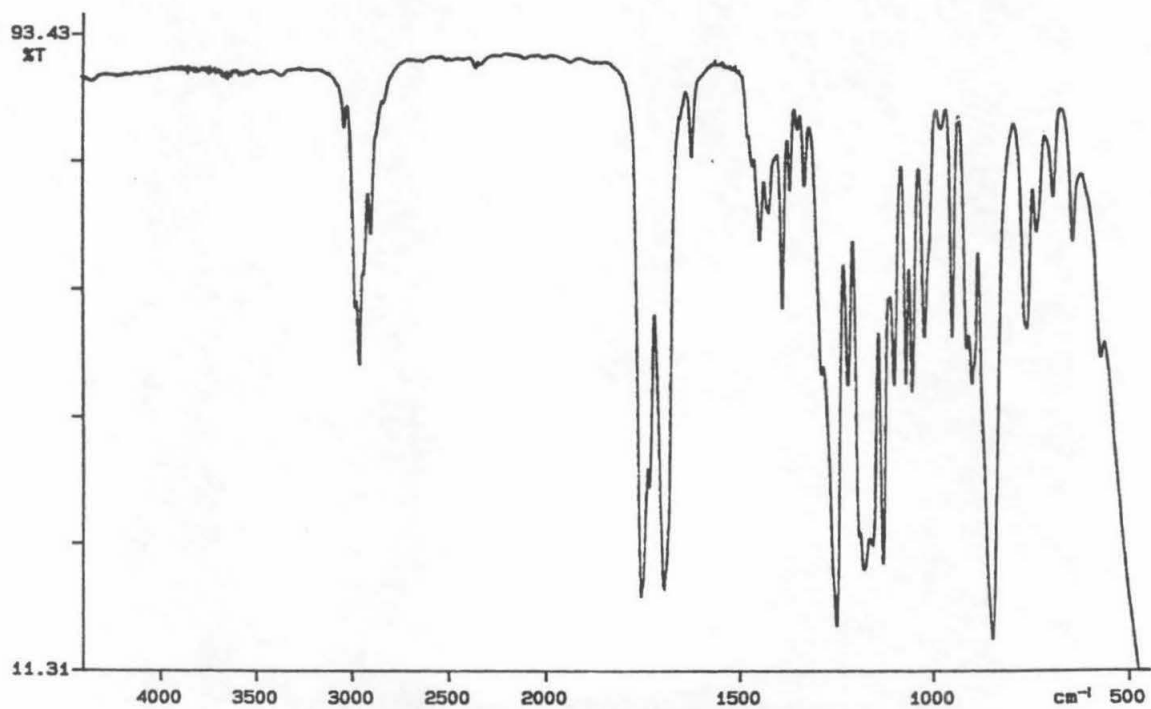
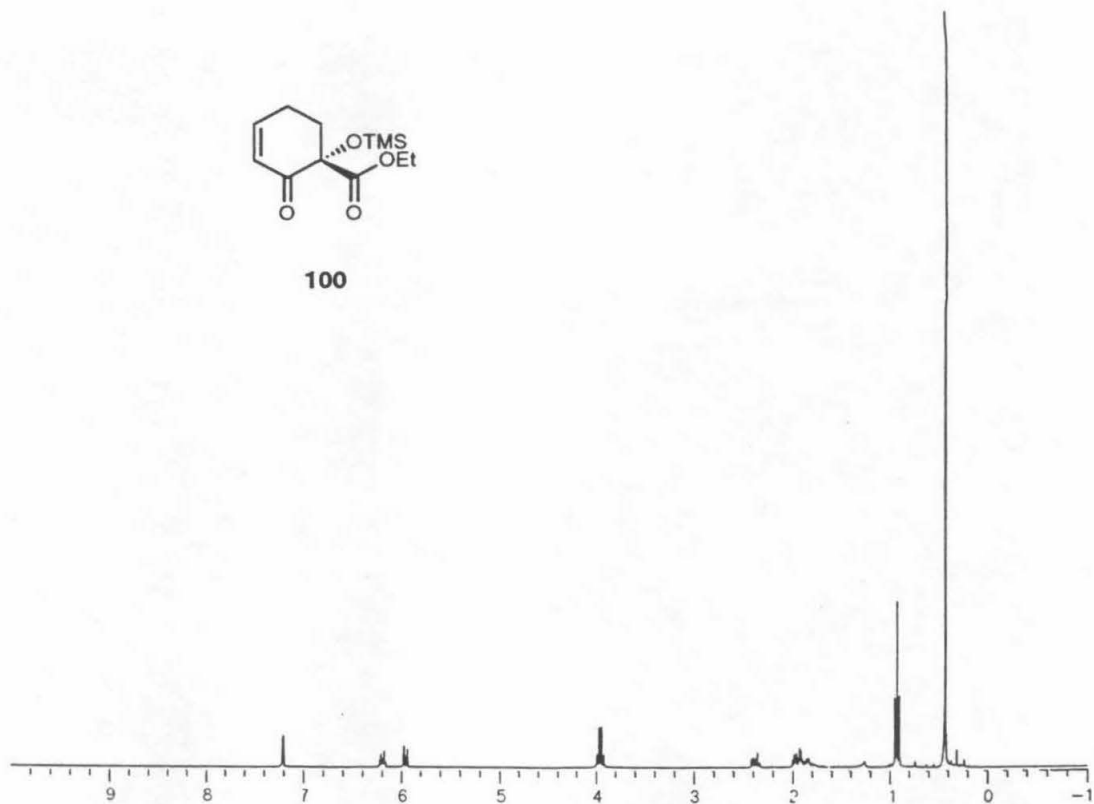


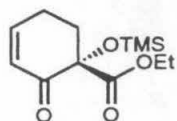
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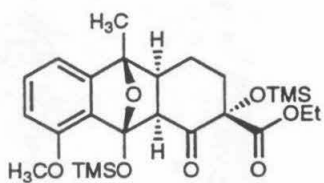
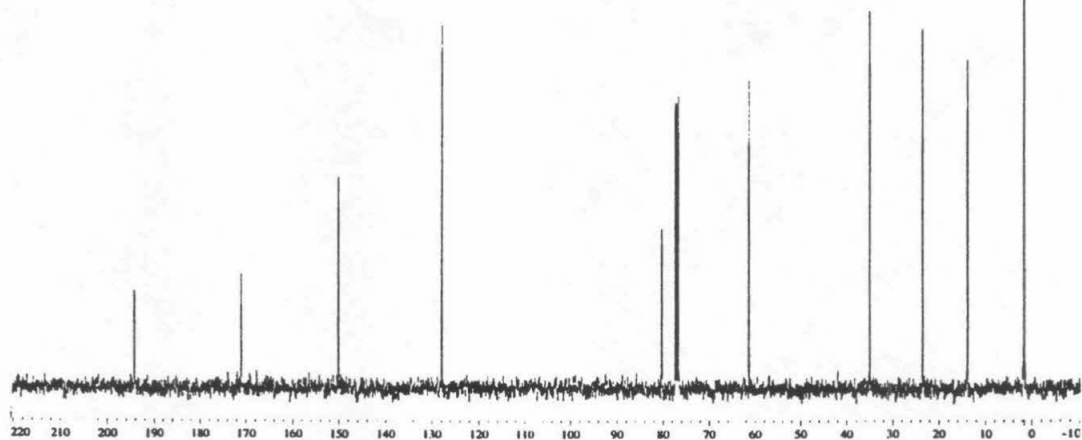


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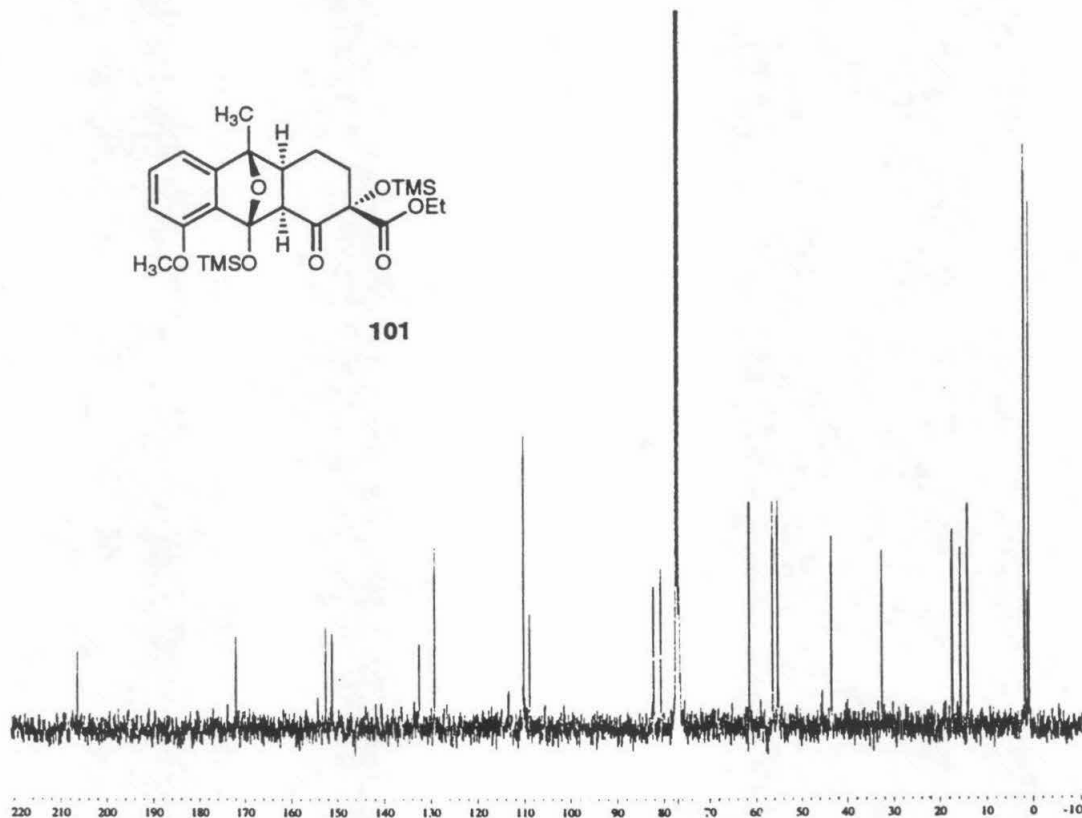




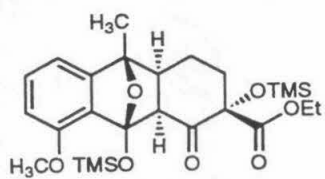
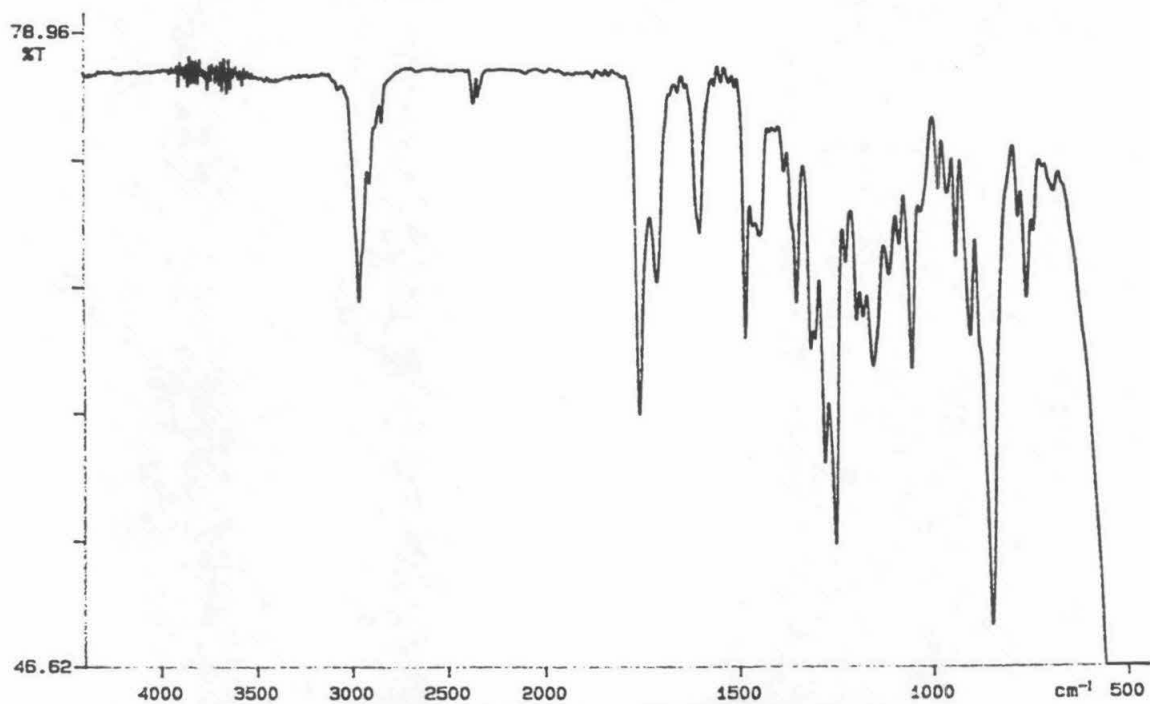
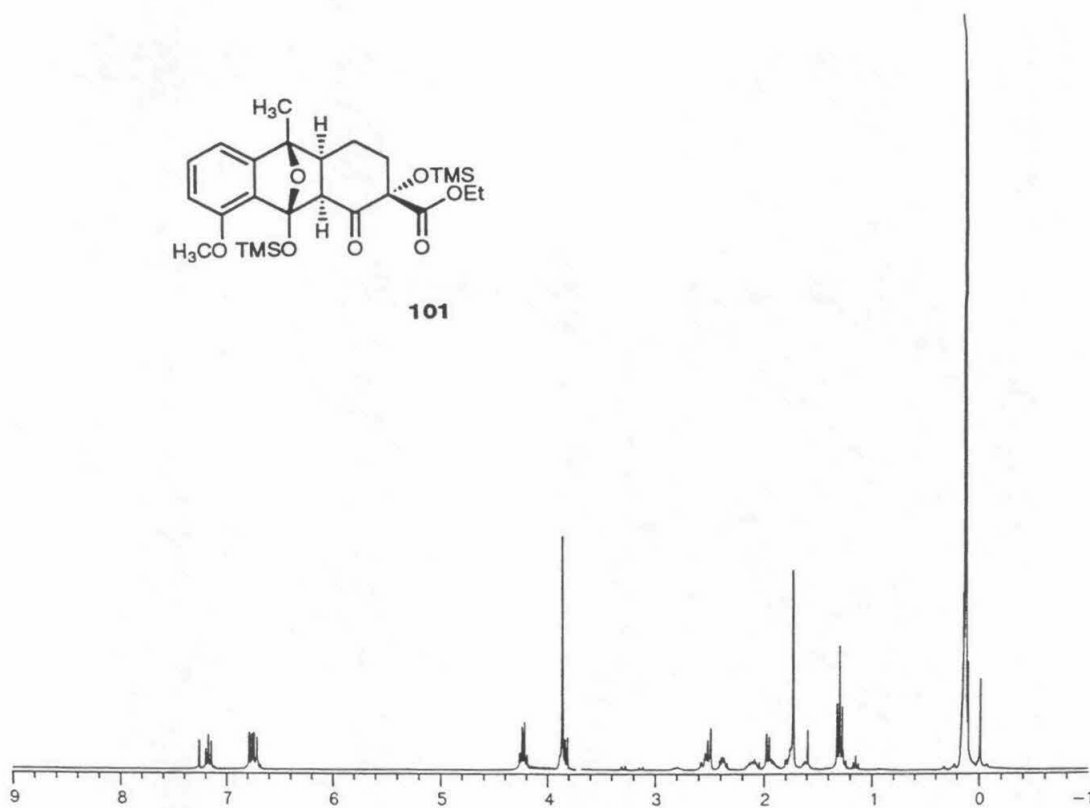
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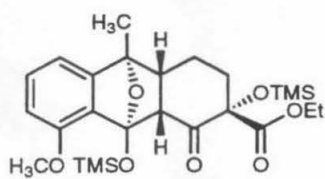


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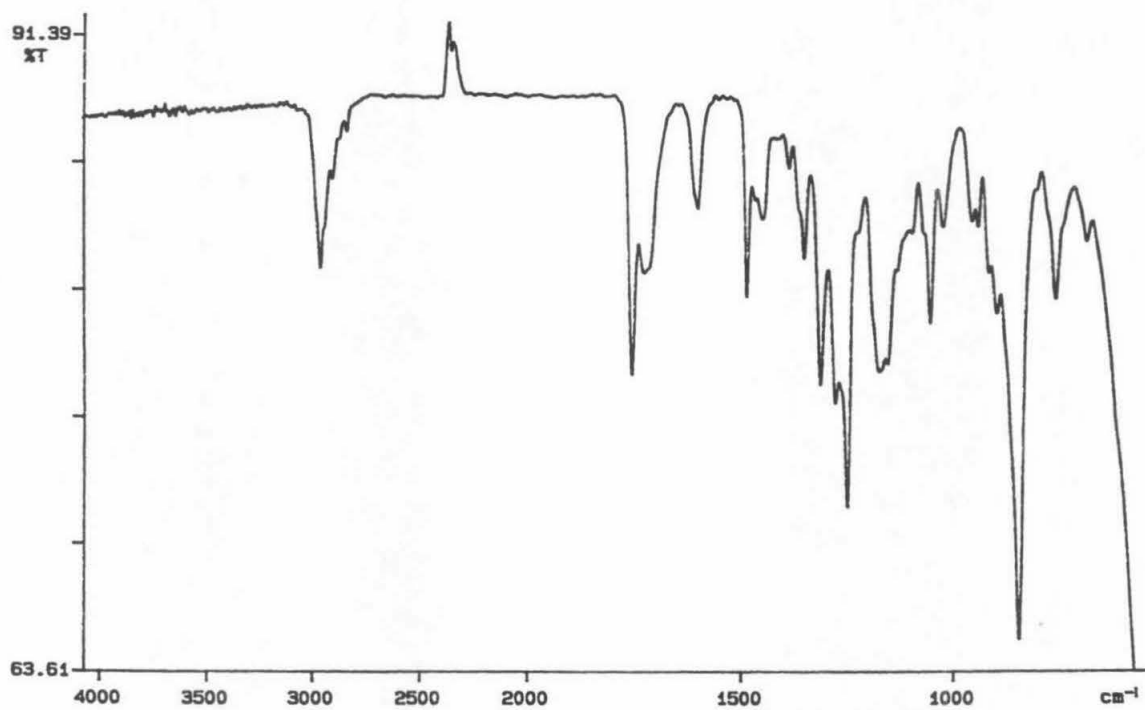
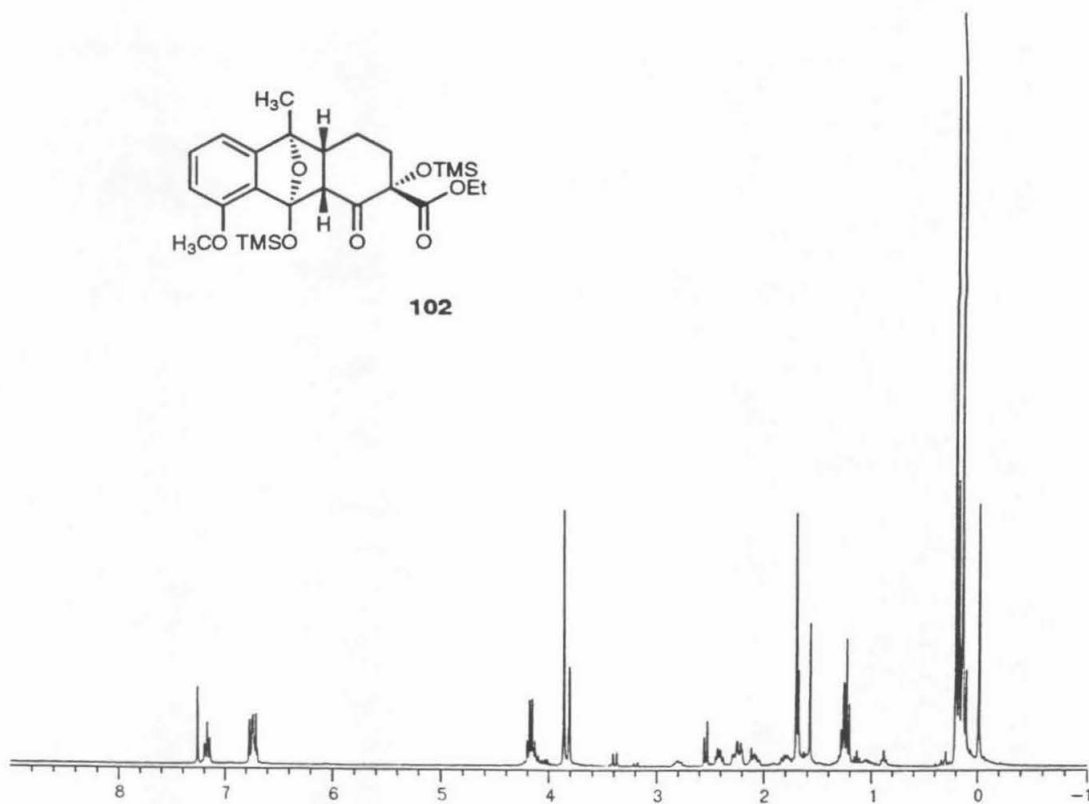


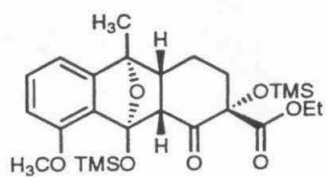


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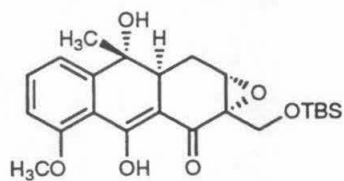
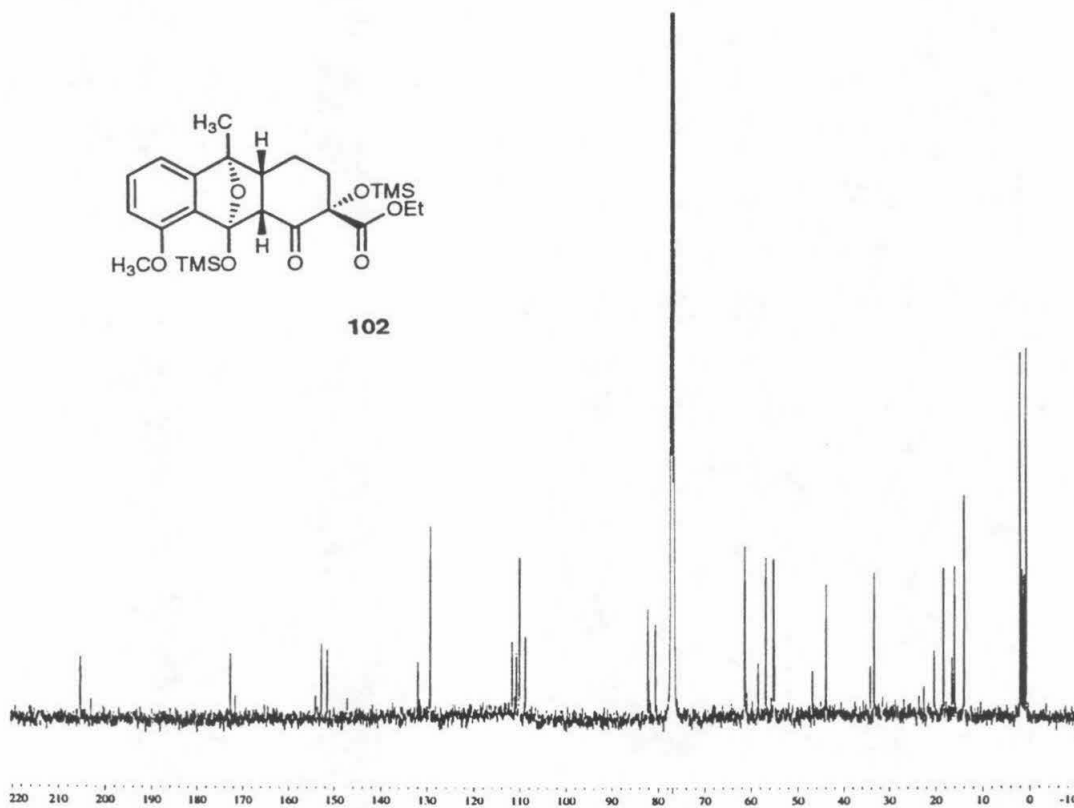


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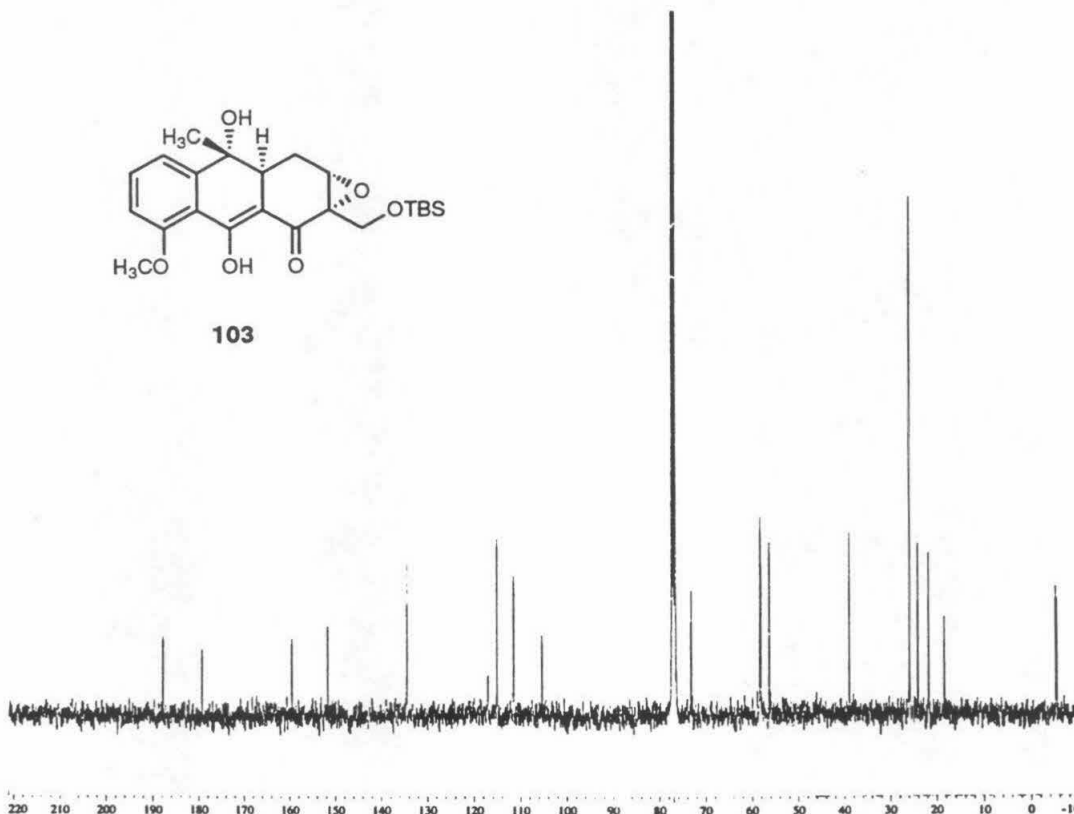




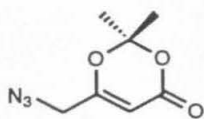
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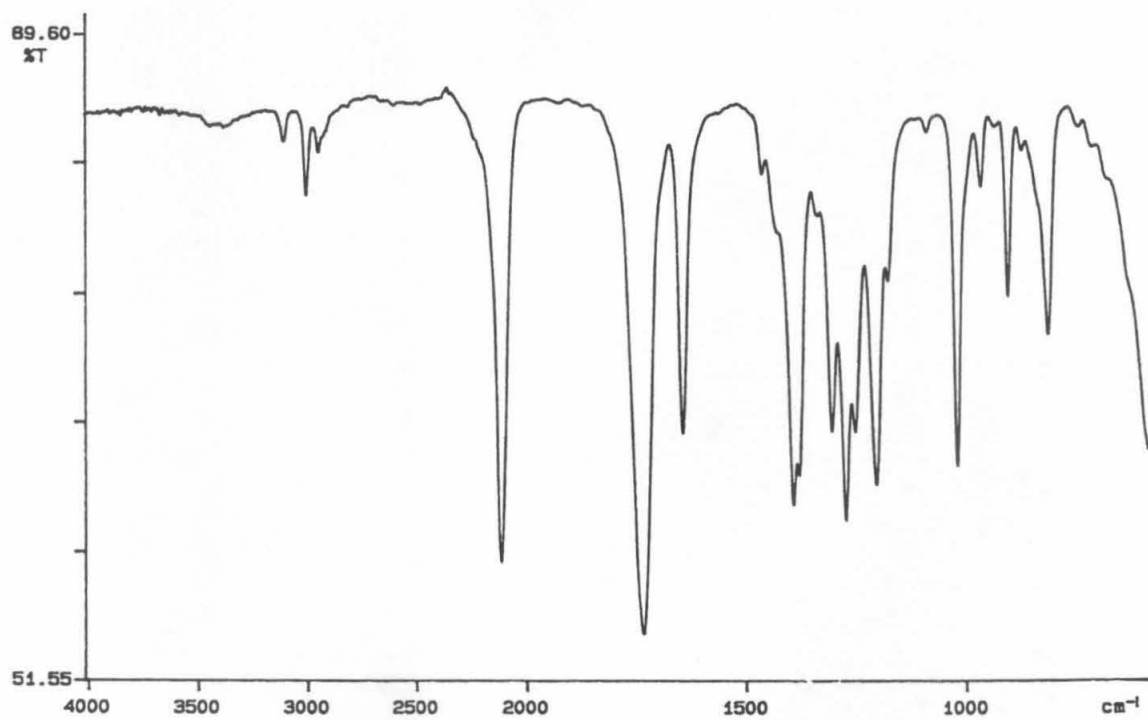
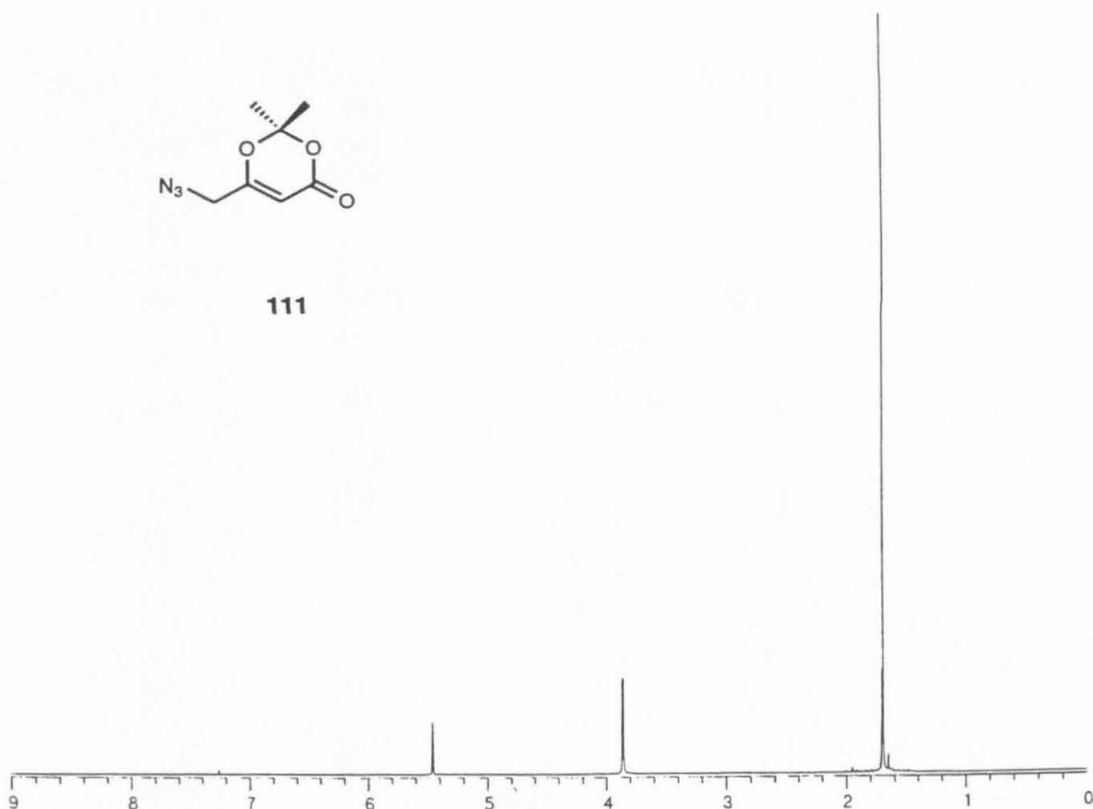
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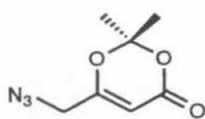




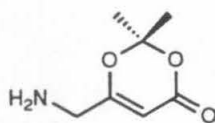
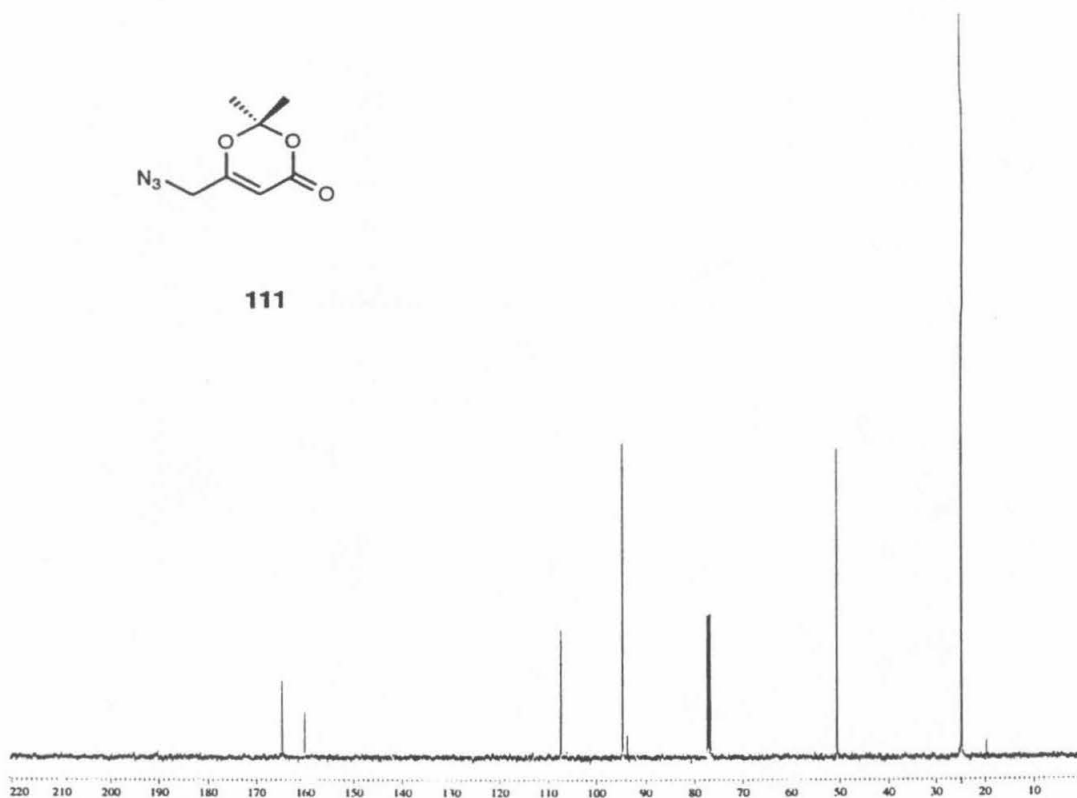


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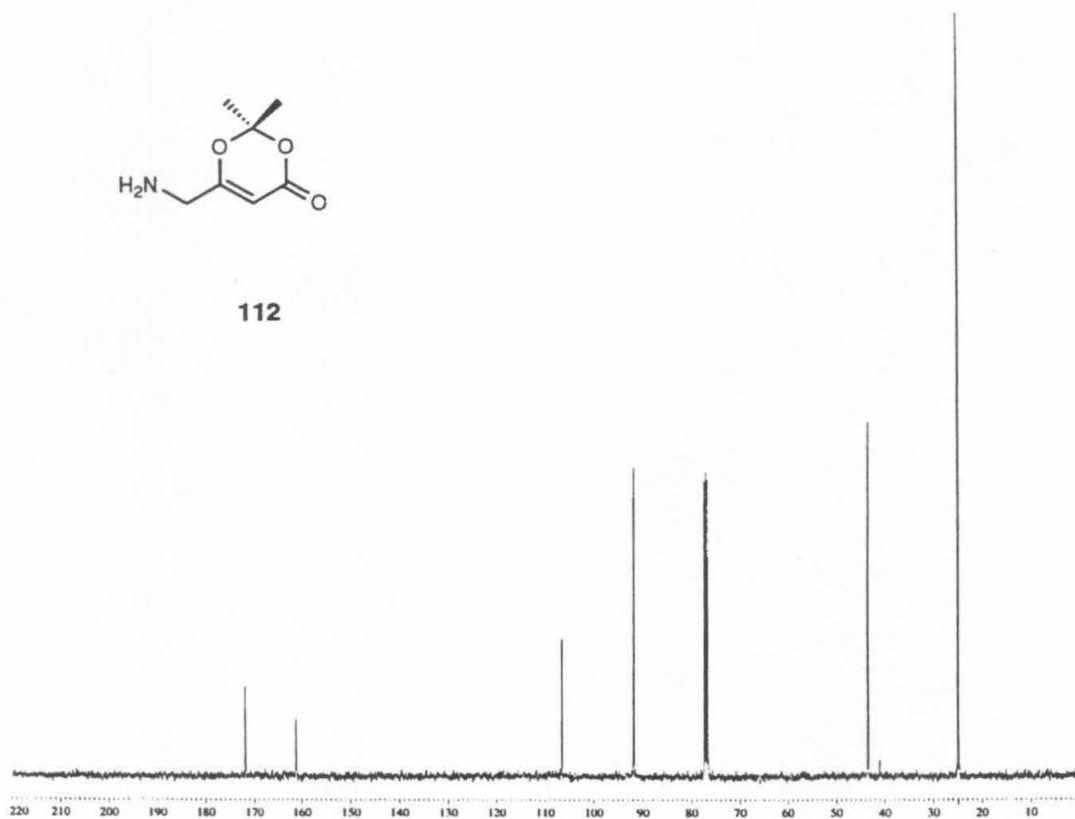


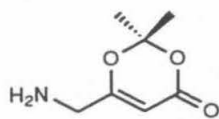


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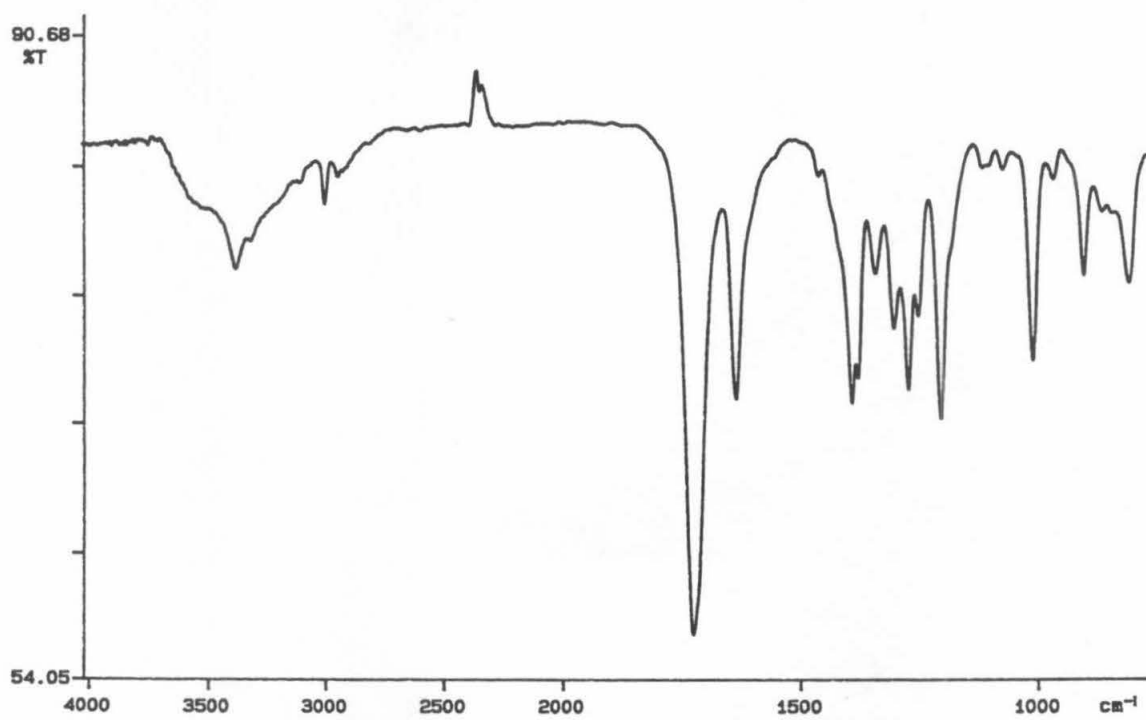
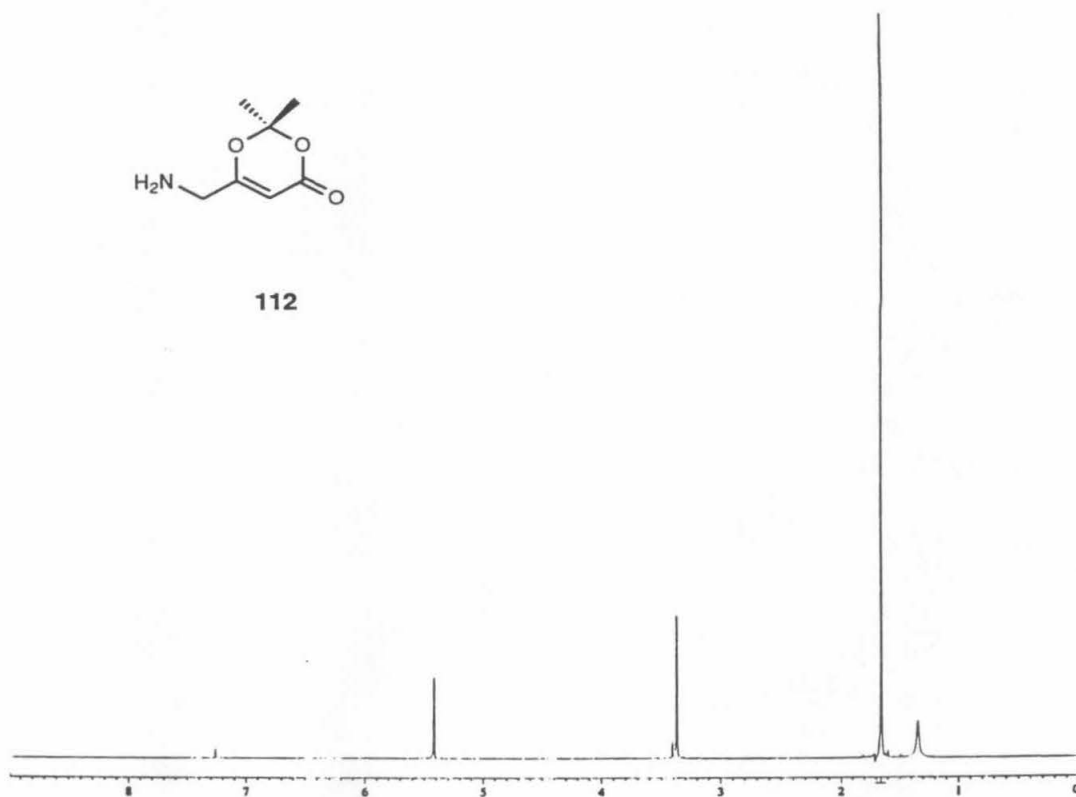


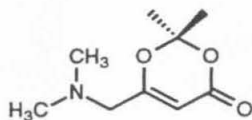
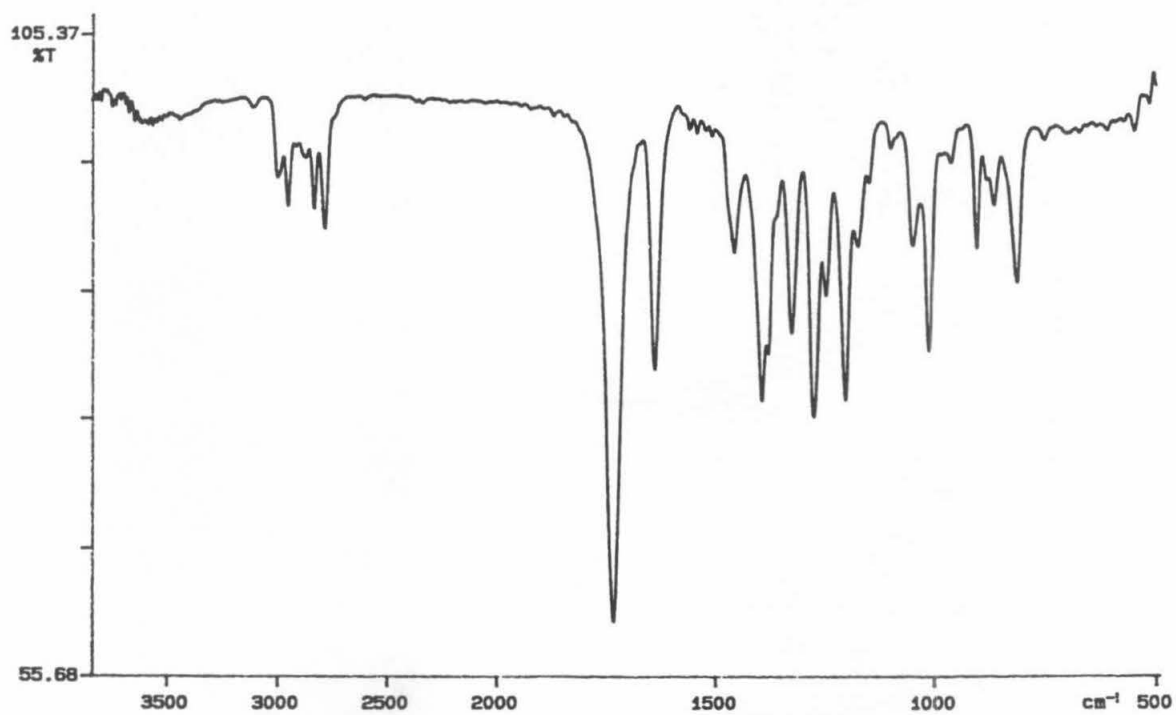
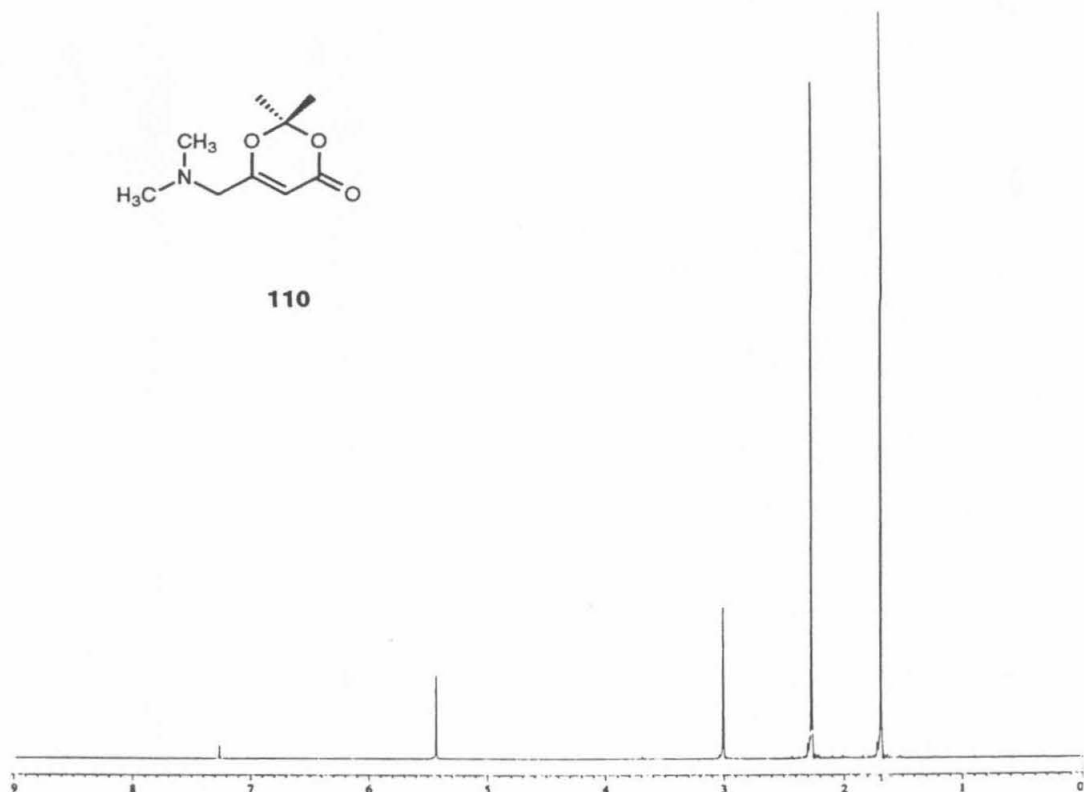
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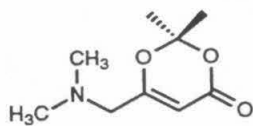
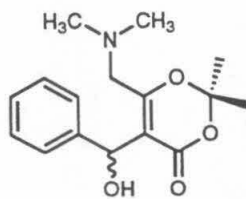
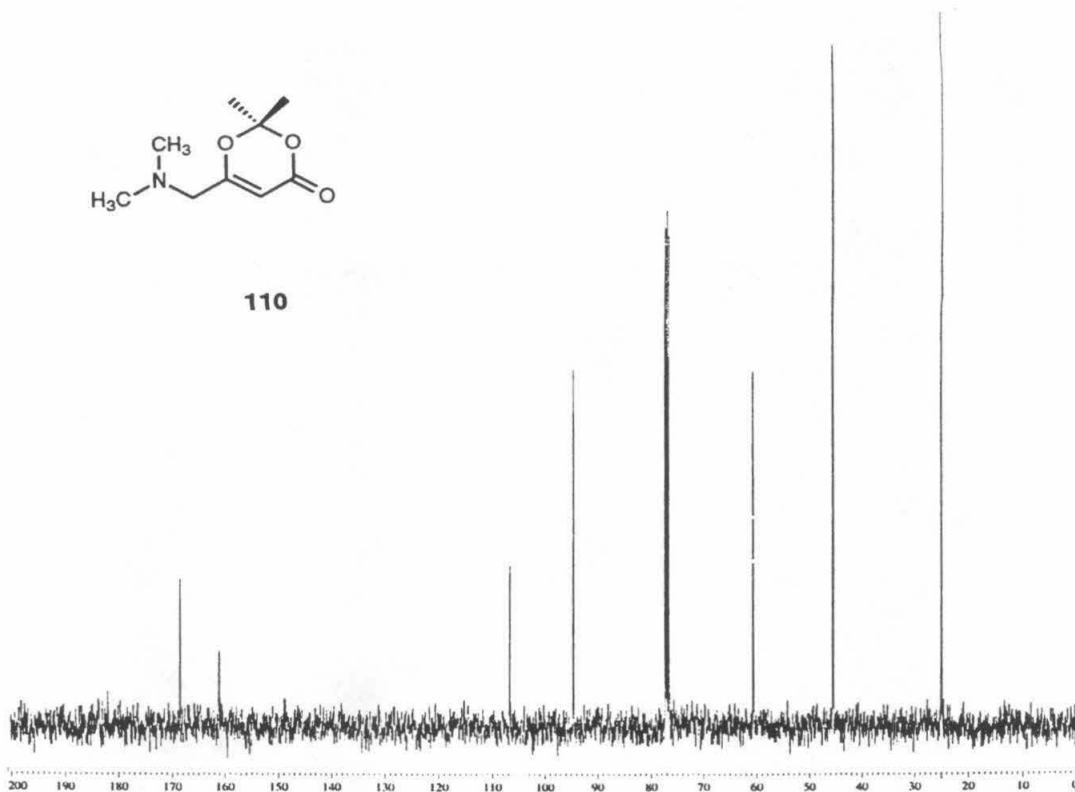
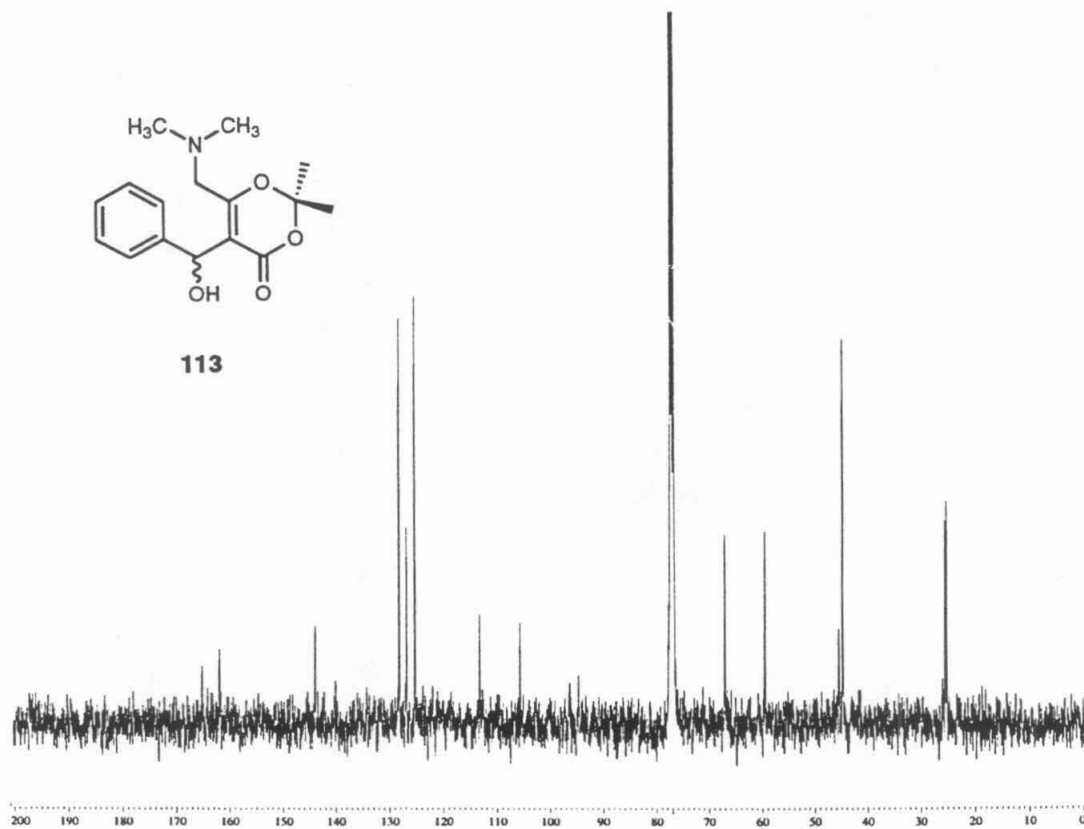


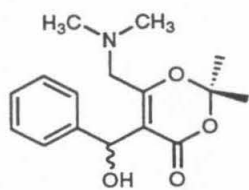
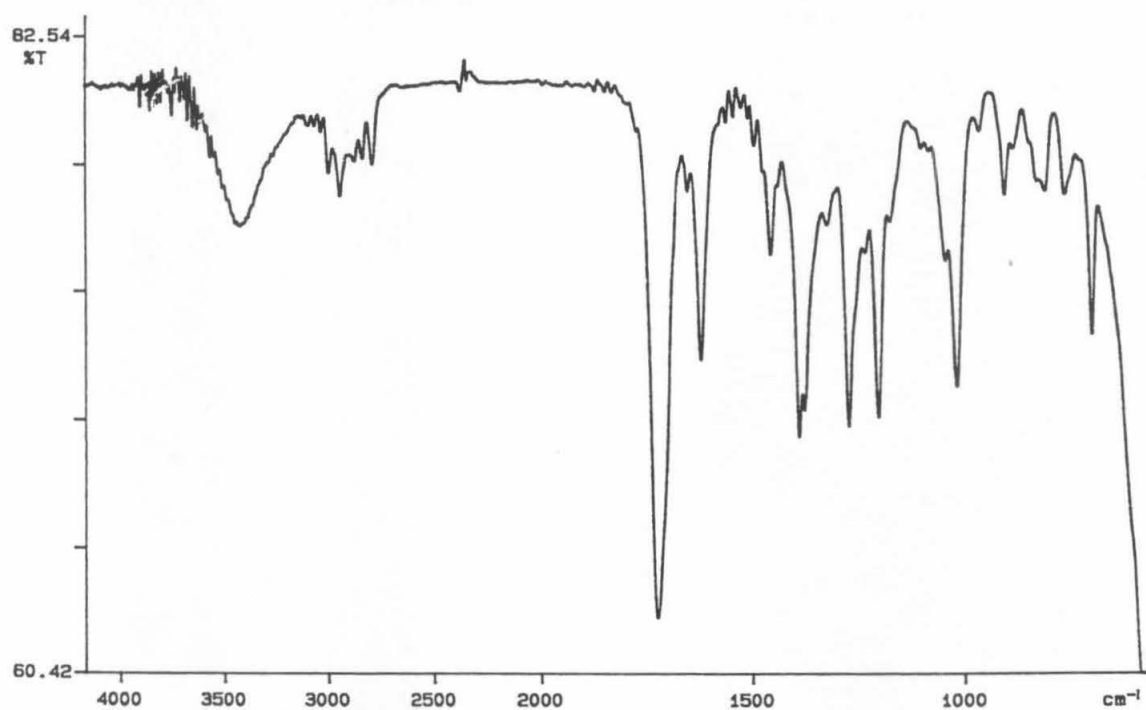
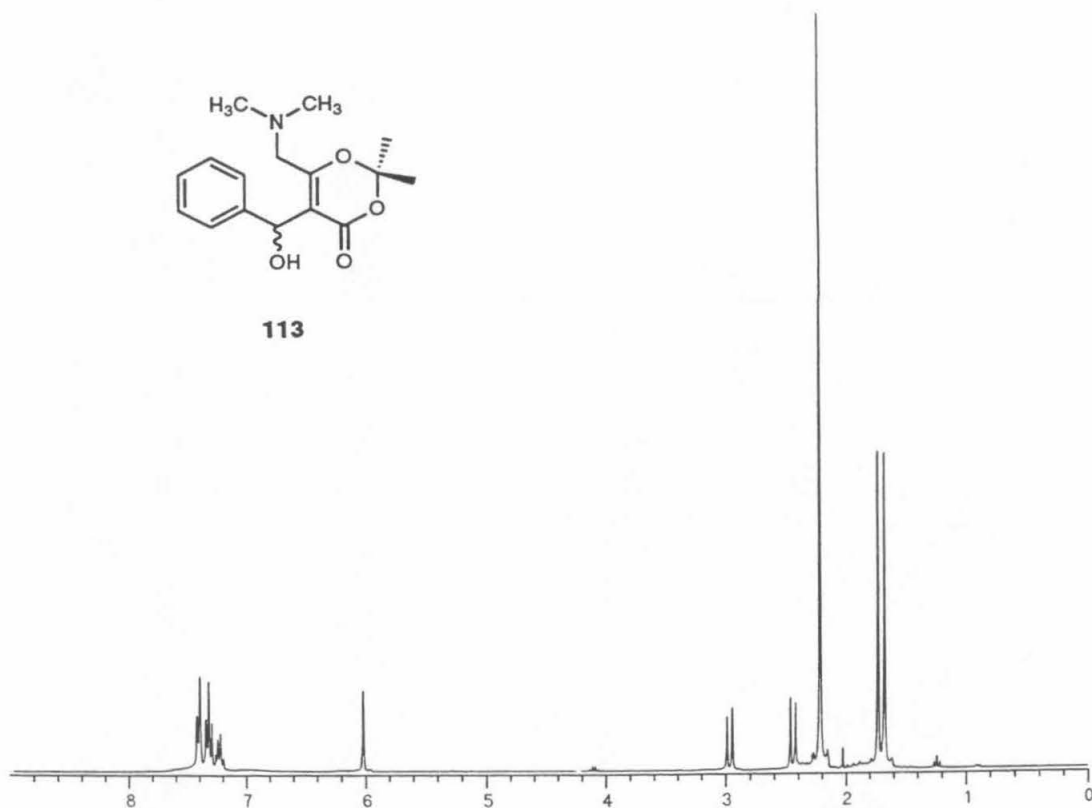
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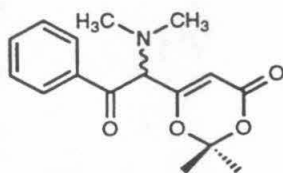


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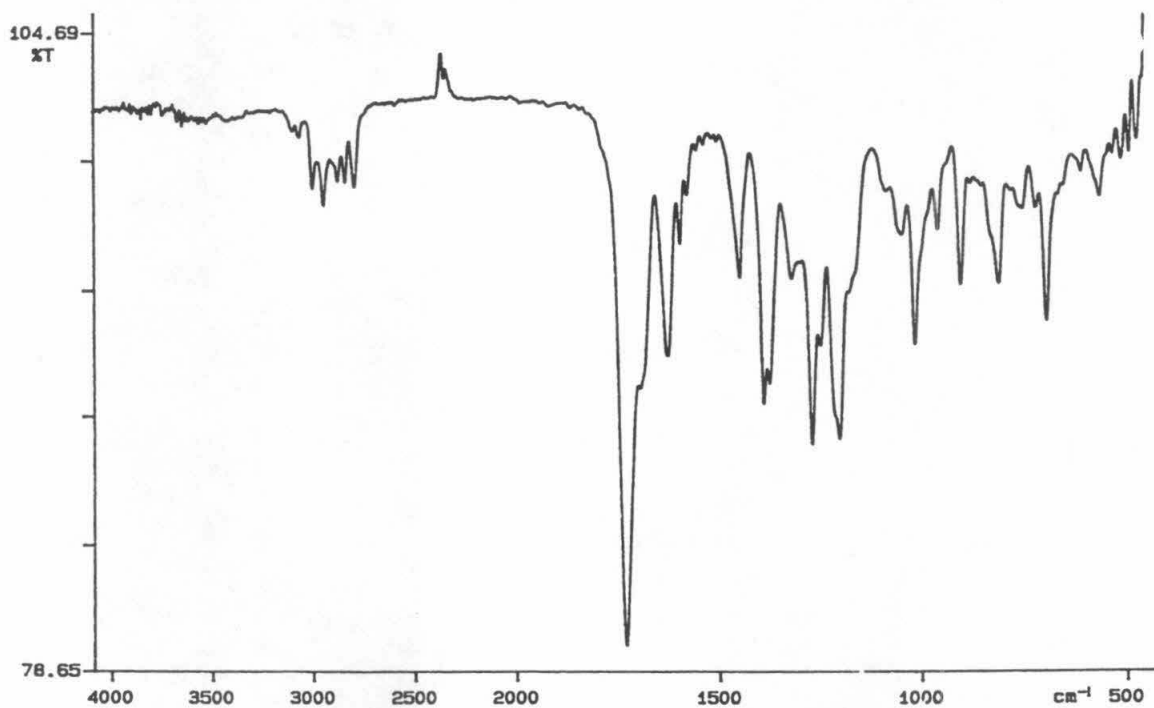
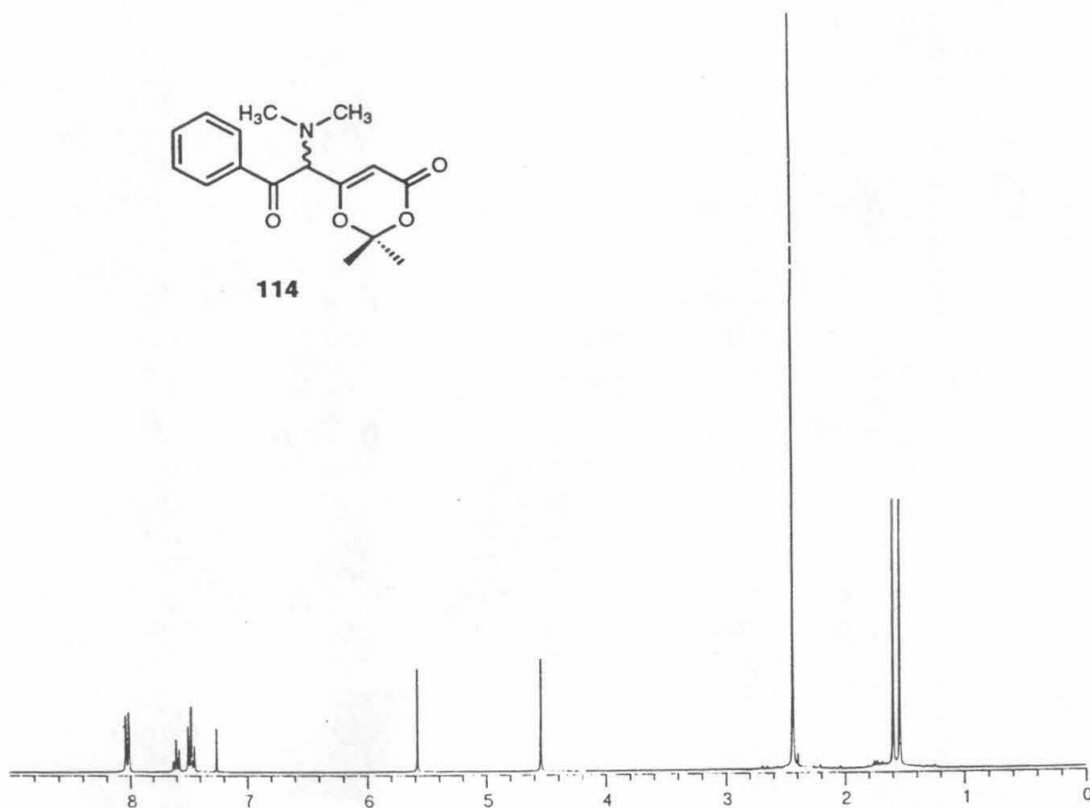


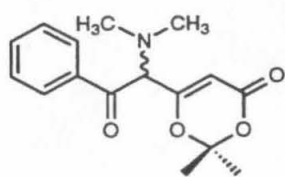
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**113**

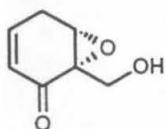
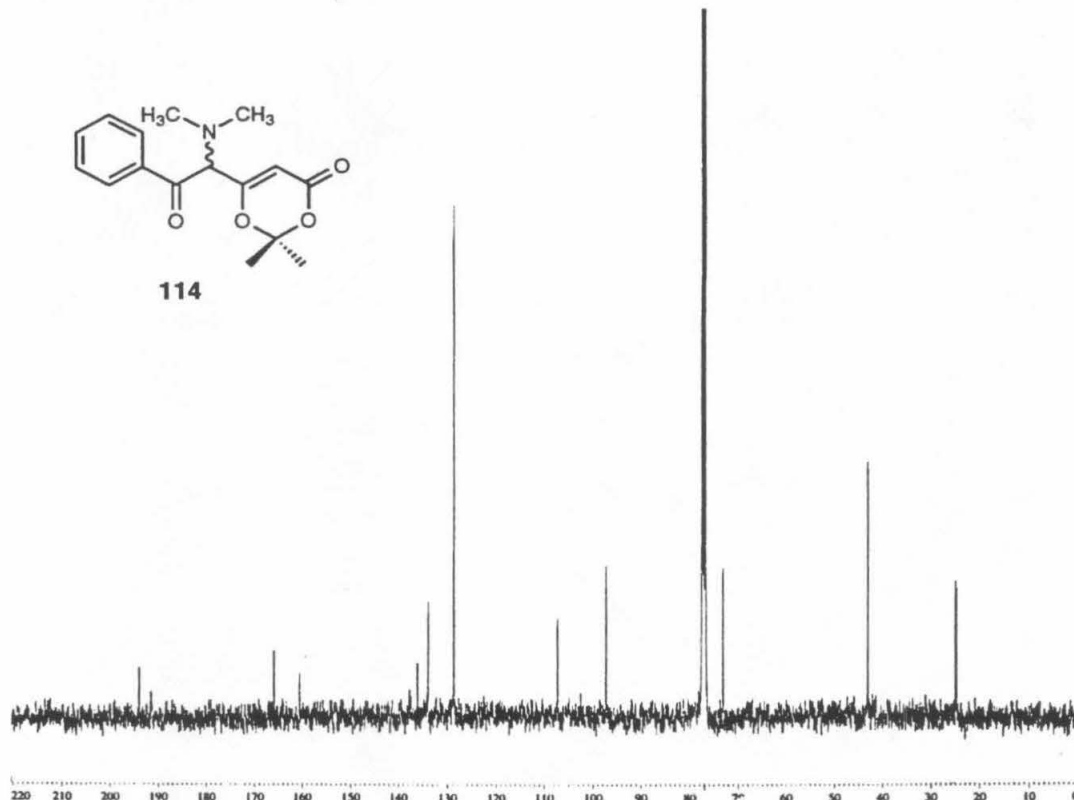


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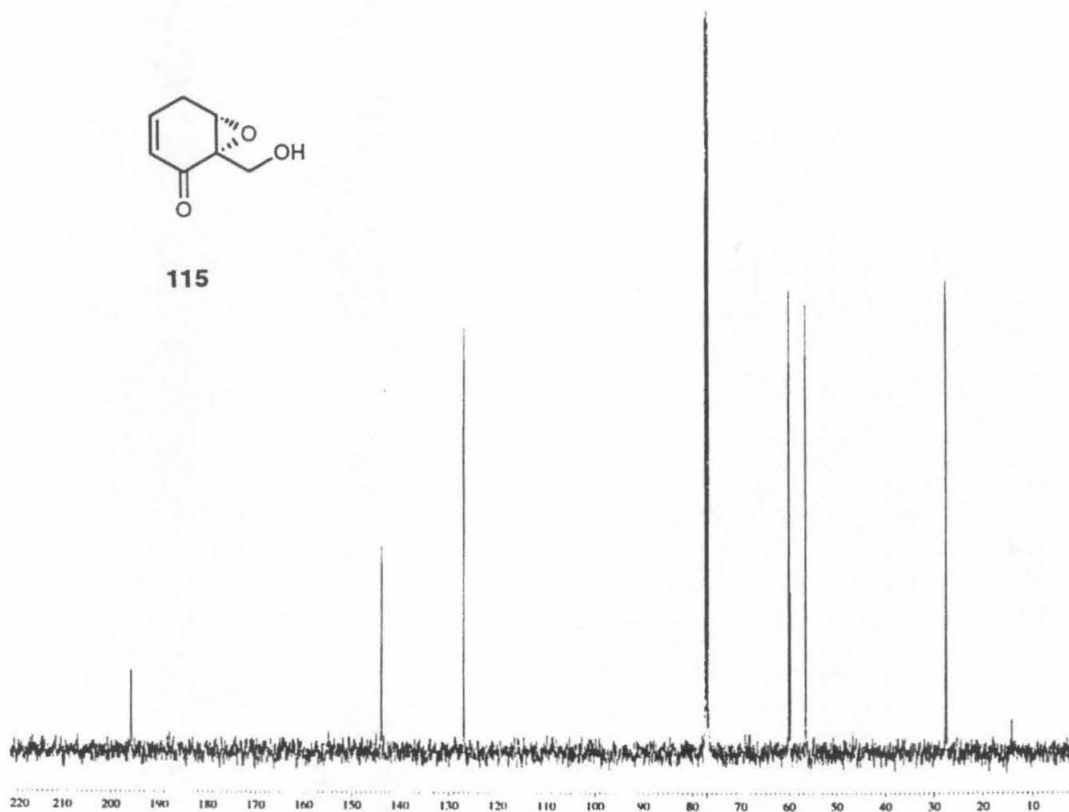


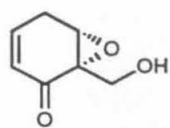


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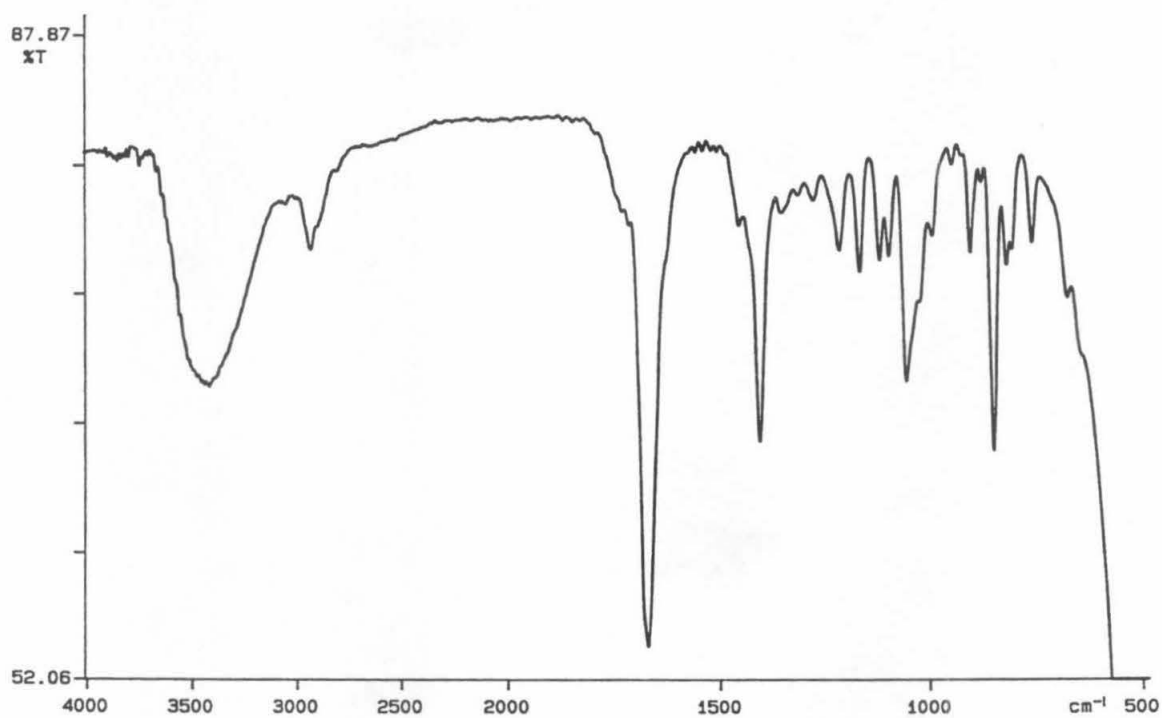
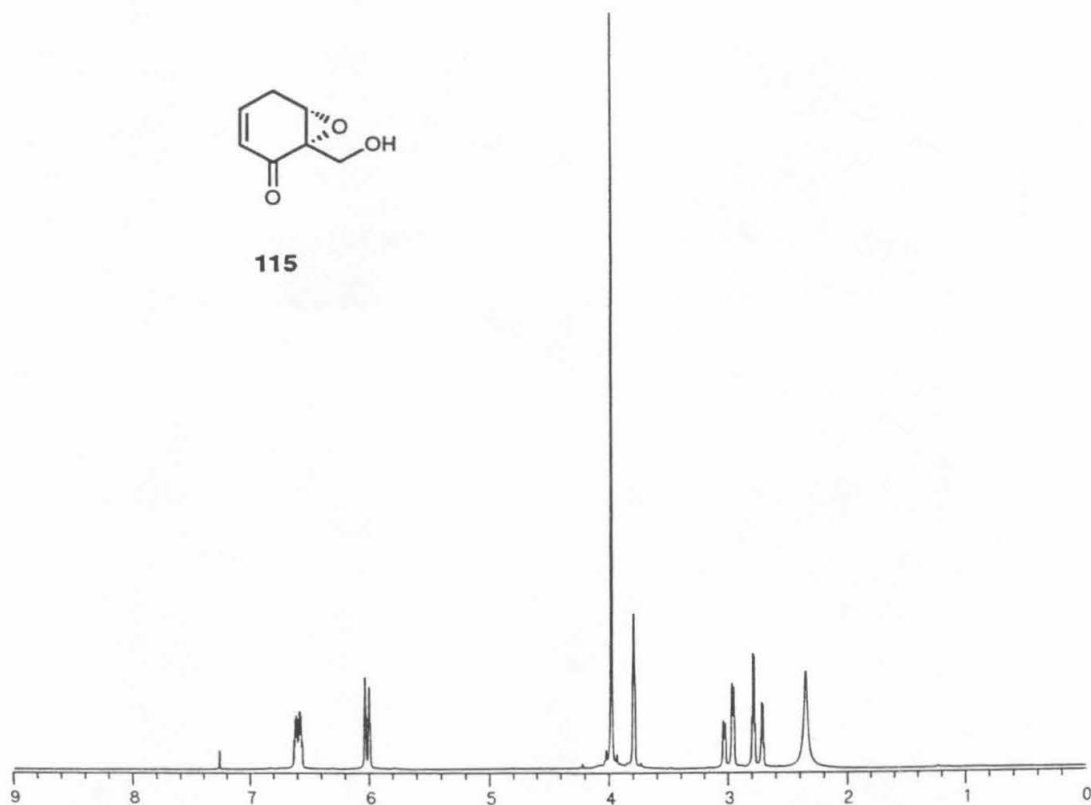


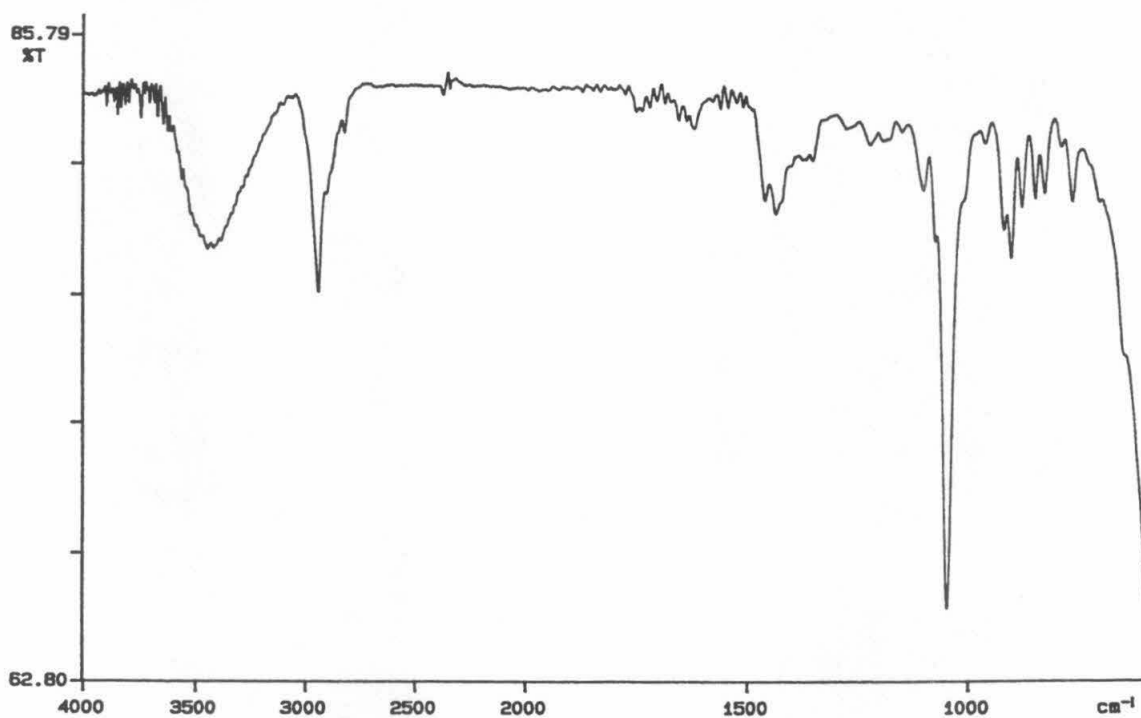
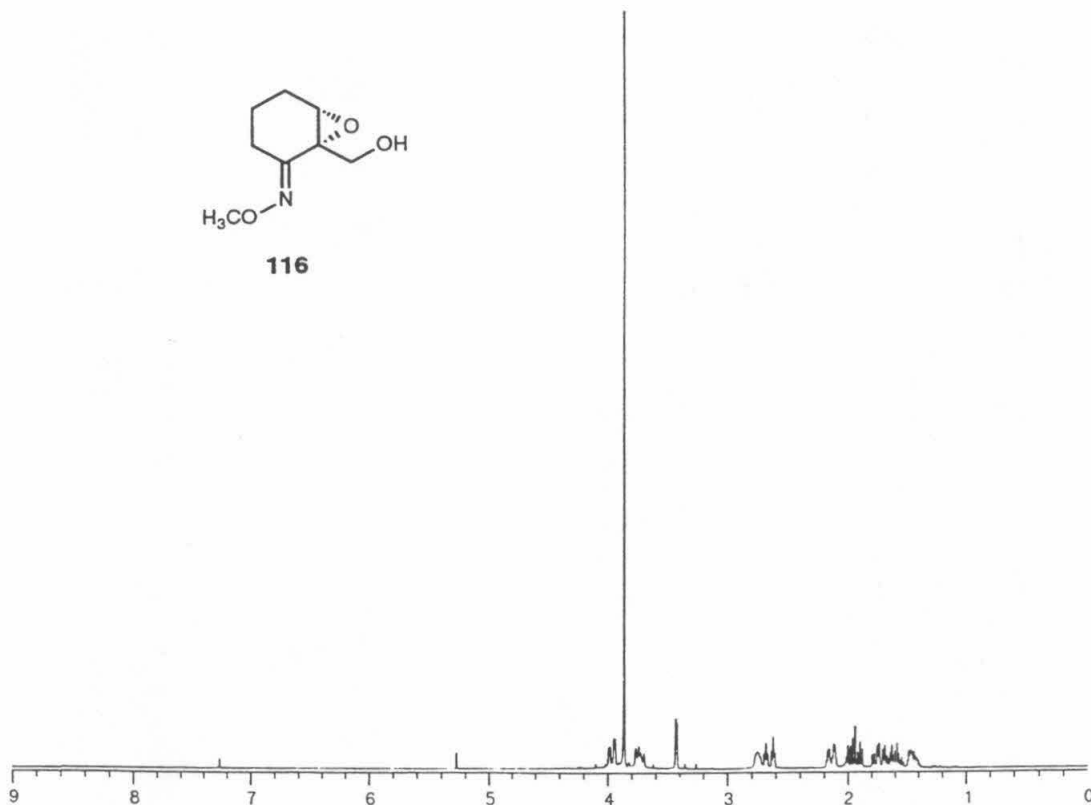
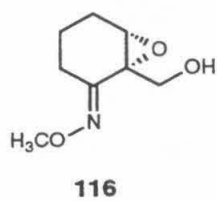
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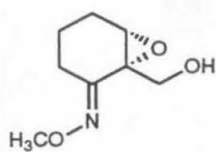
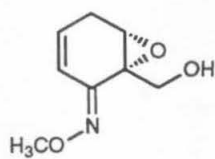
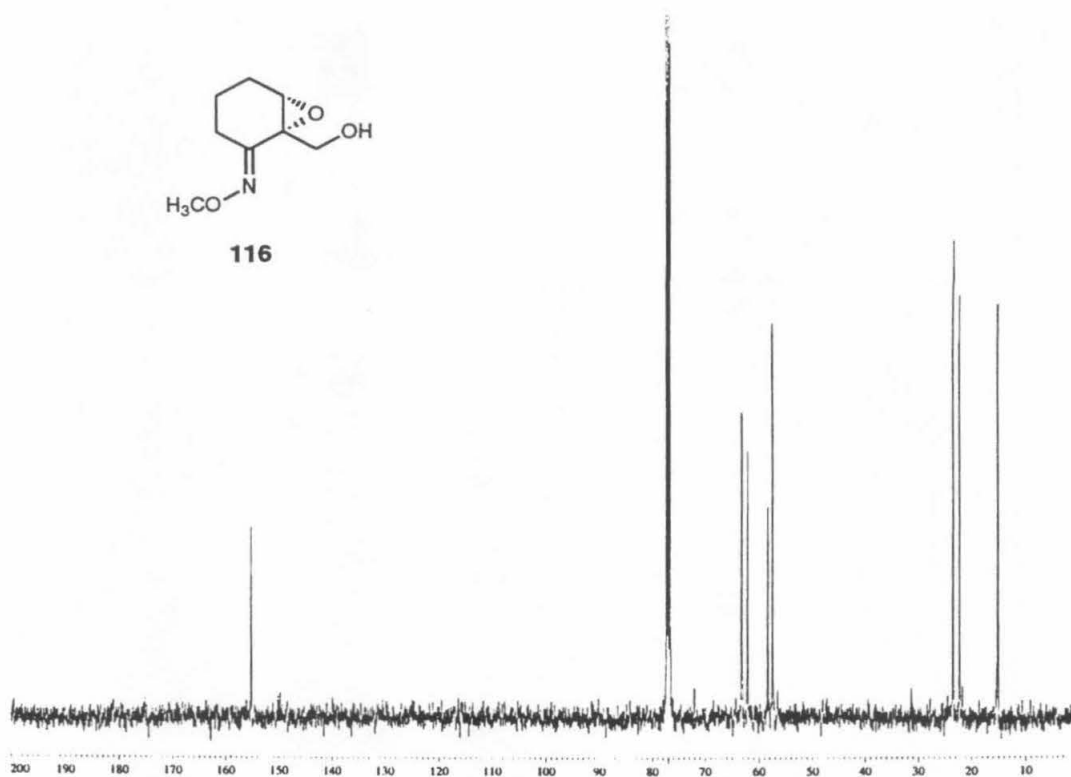
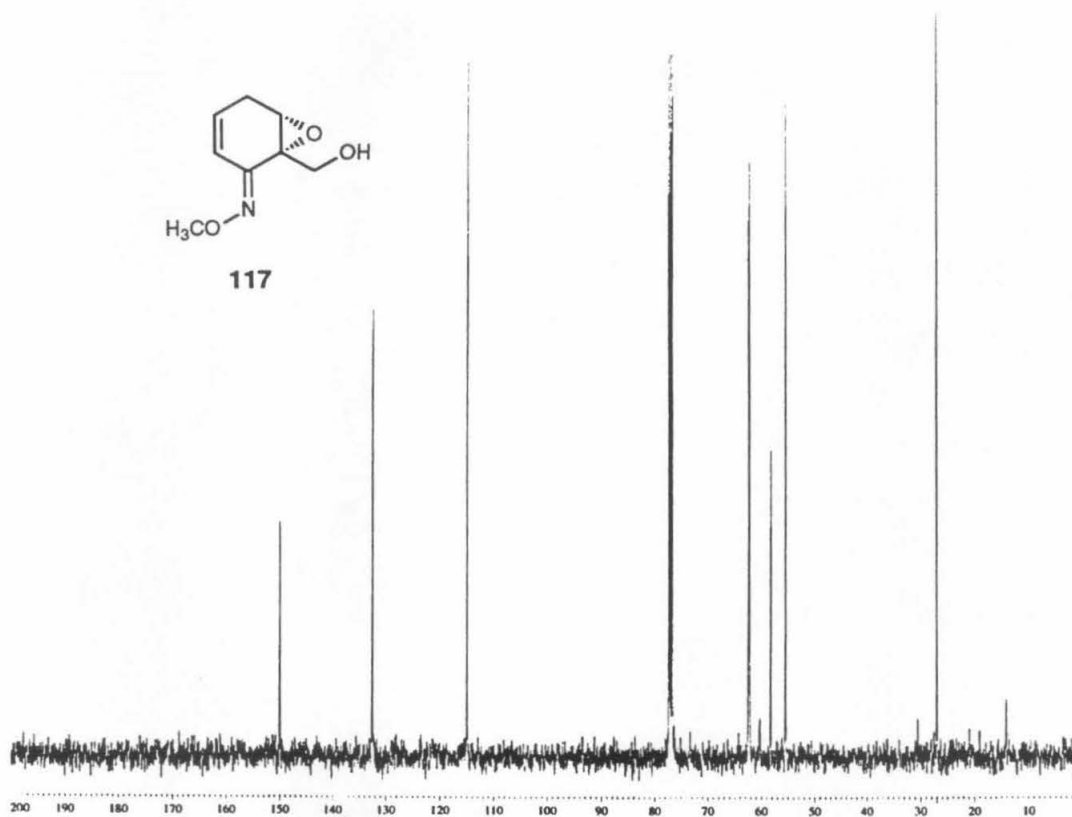


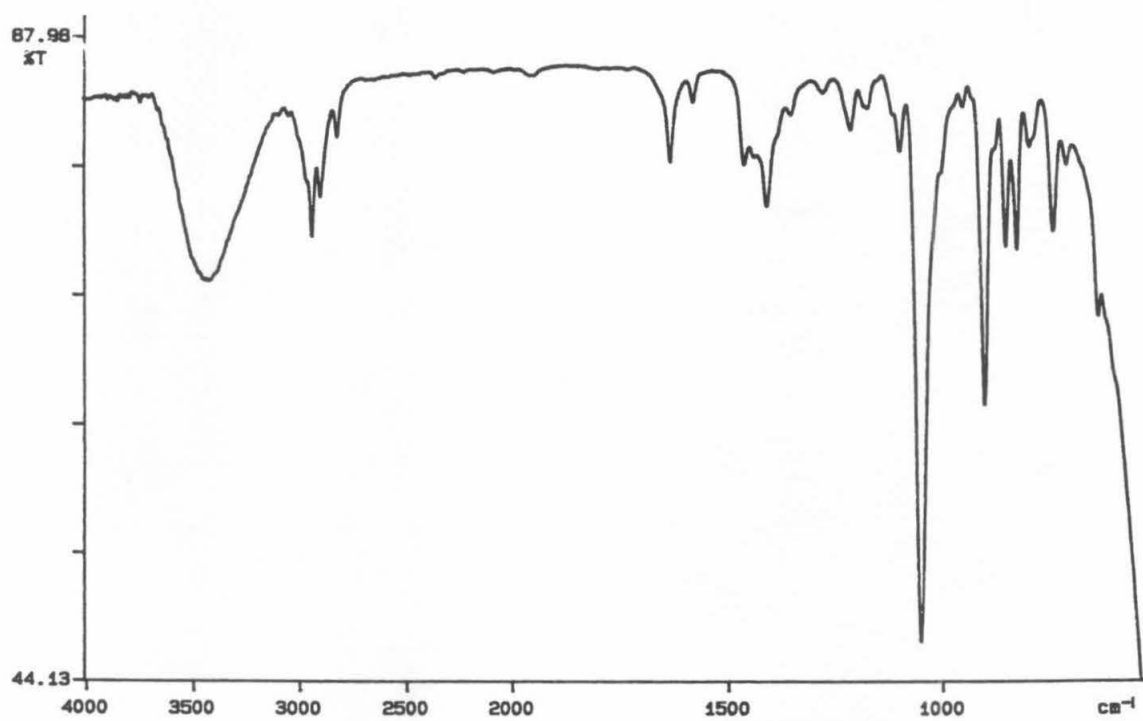
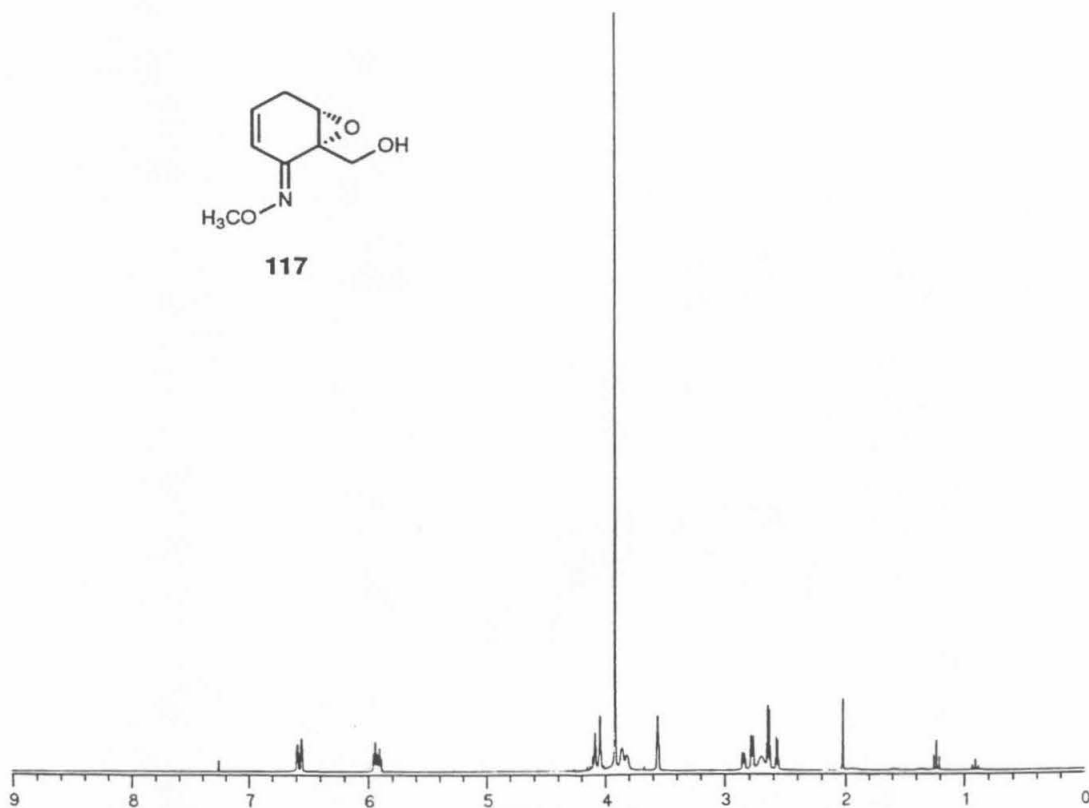
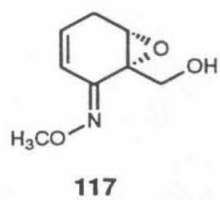


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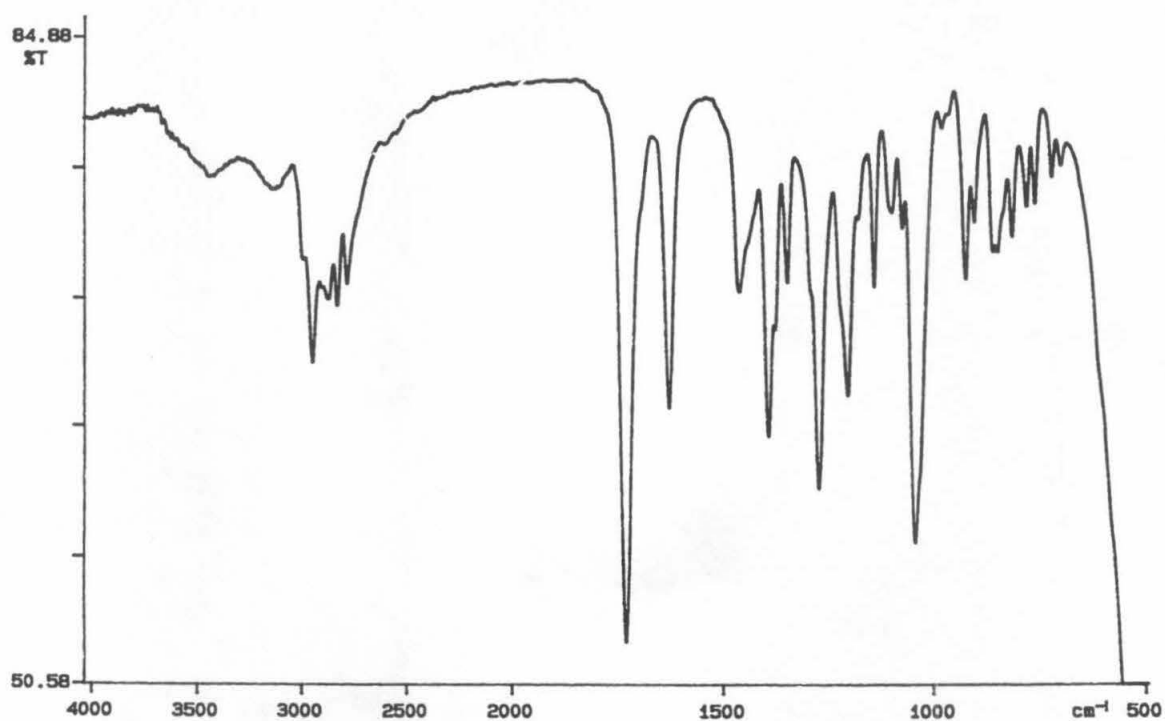
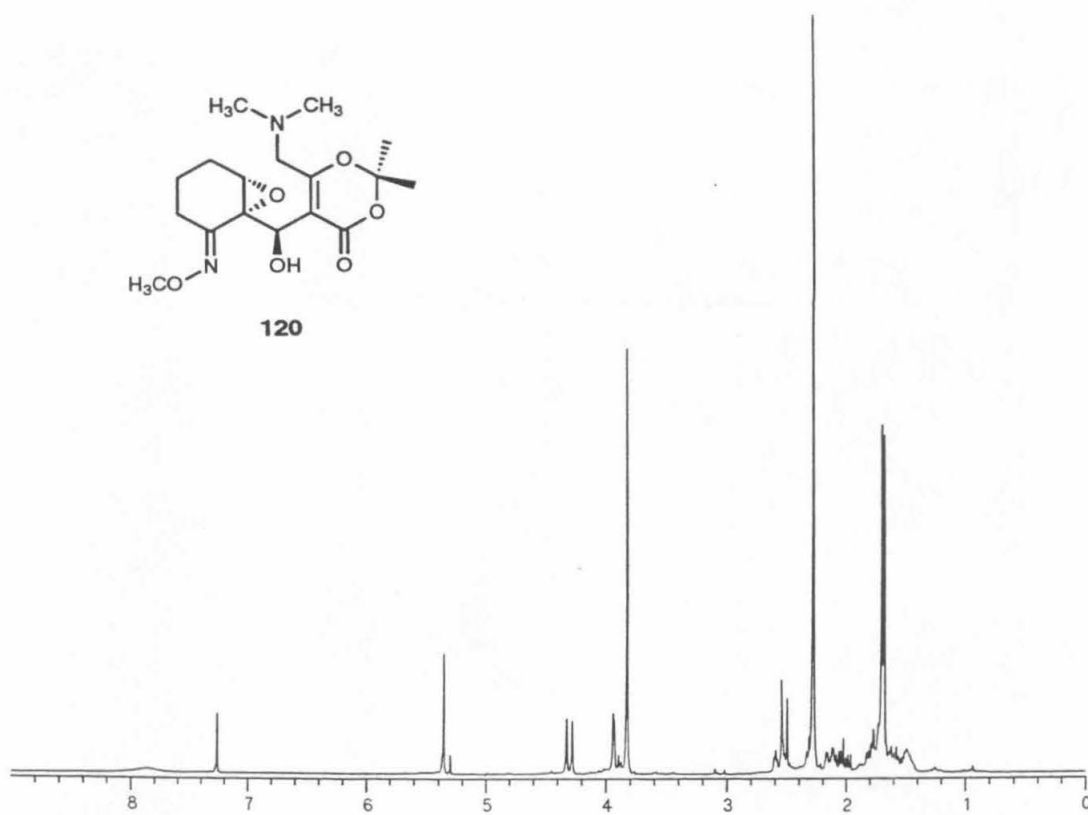
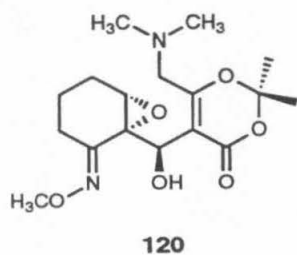


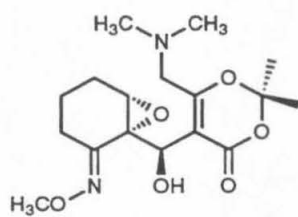
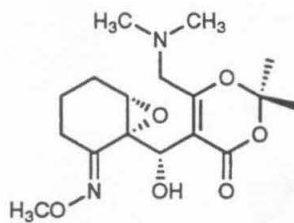
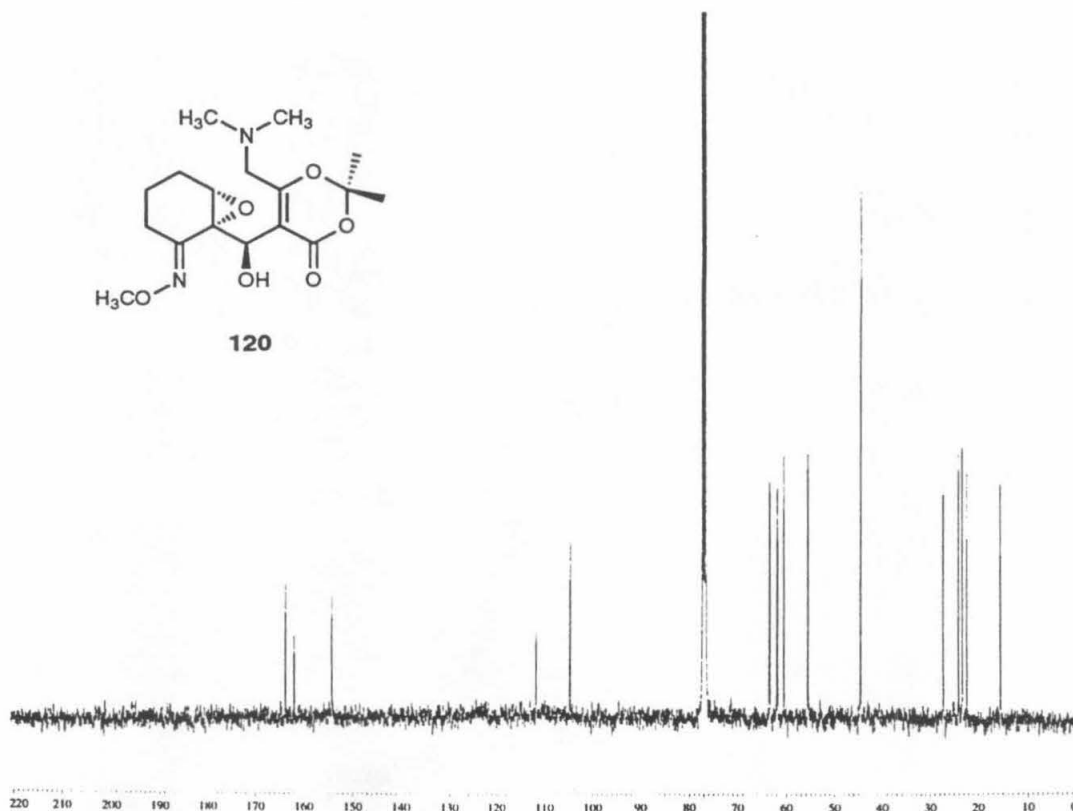
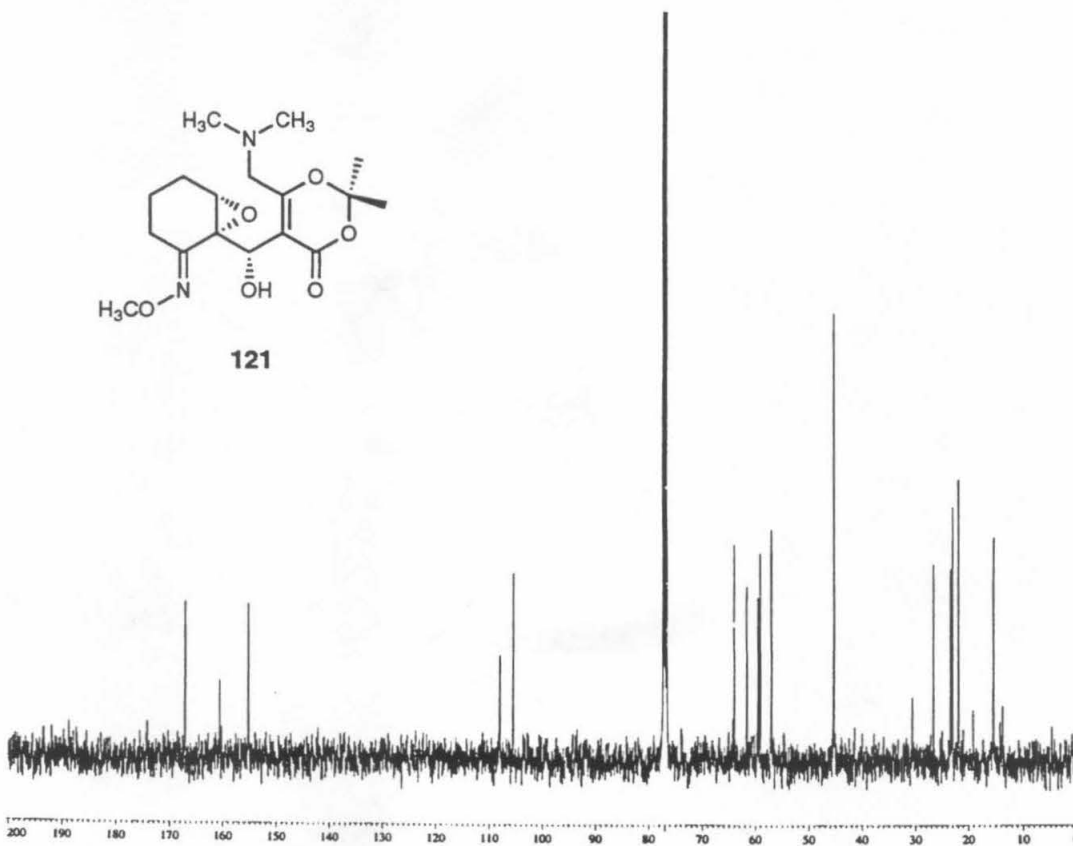


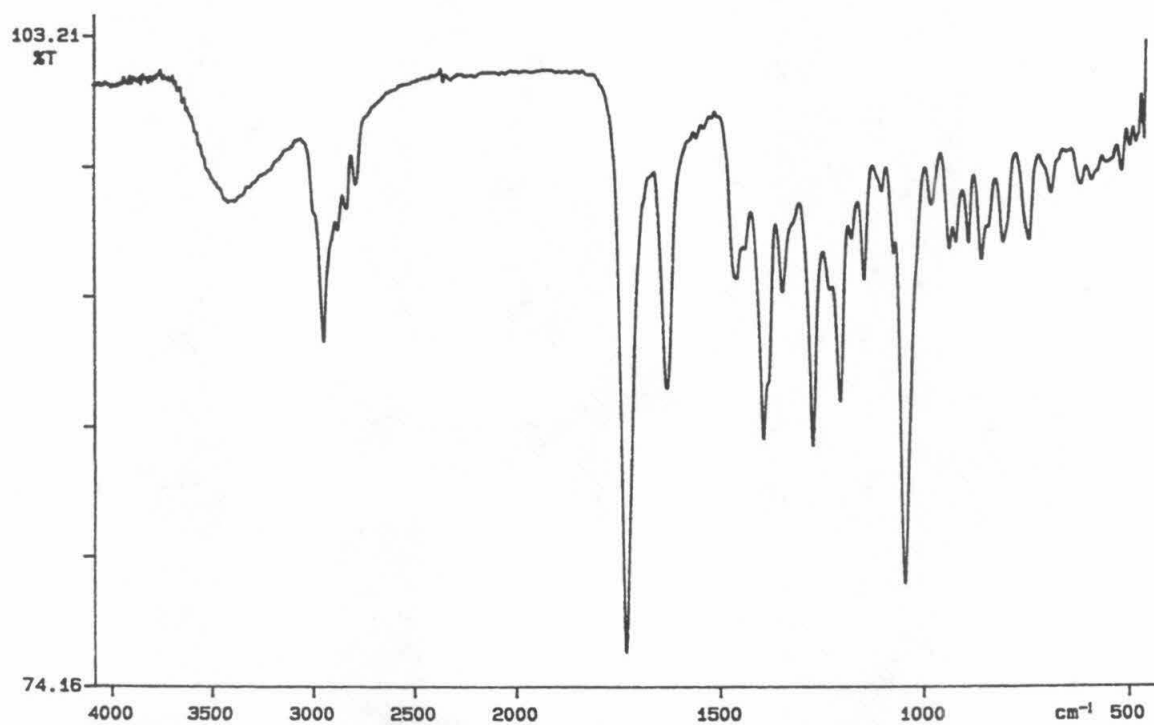
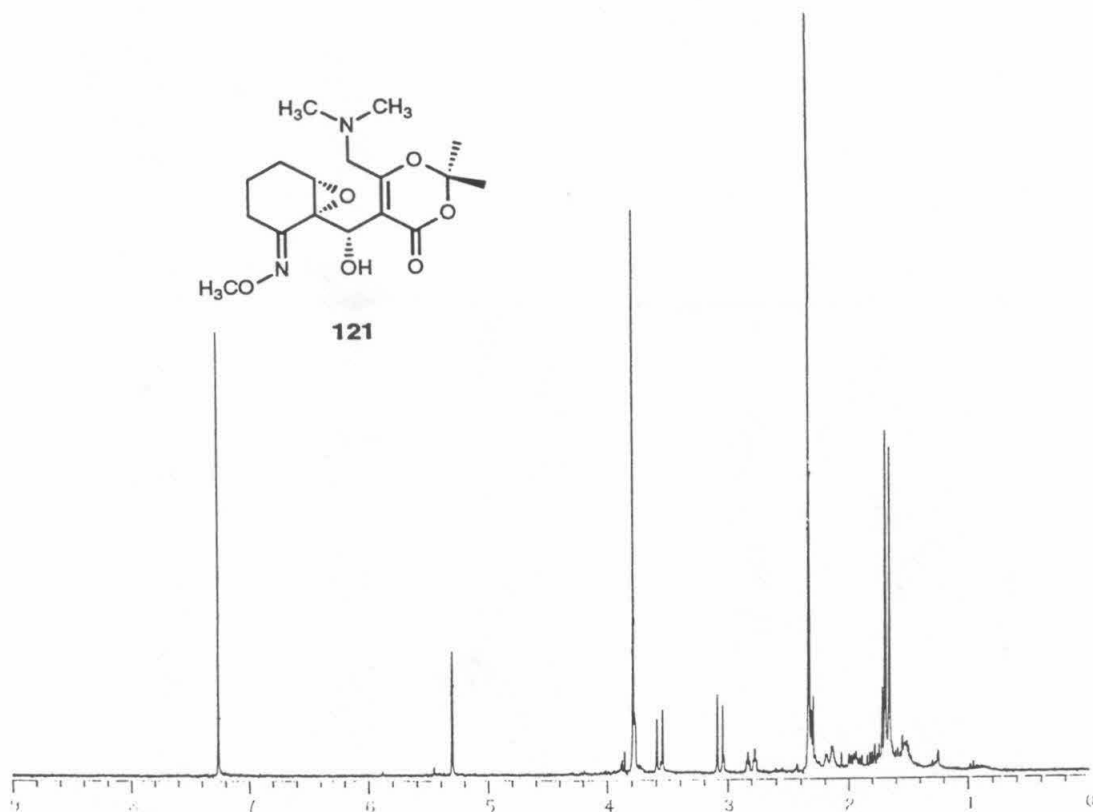
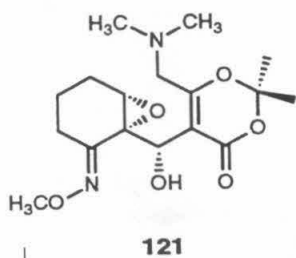
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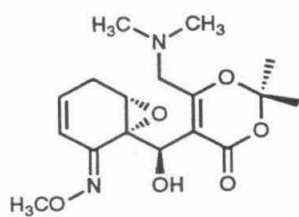




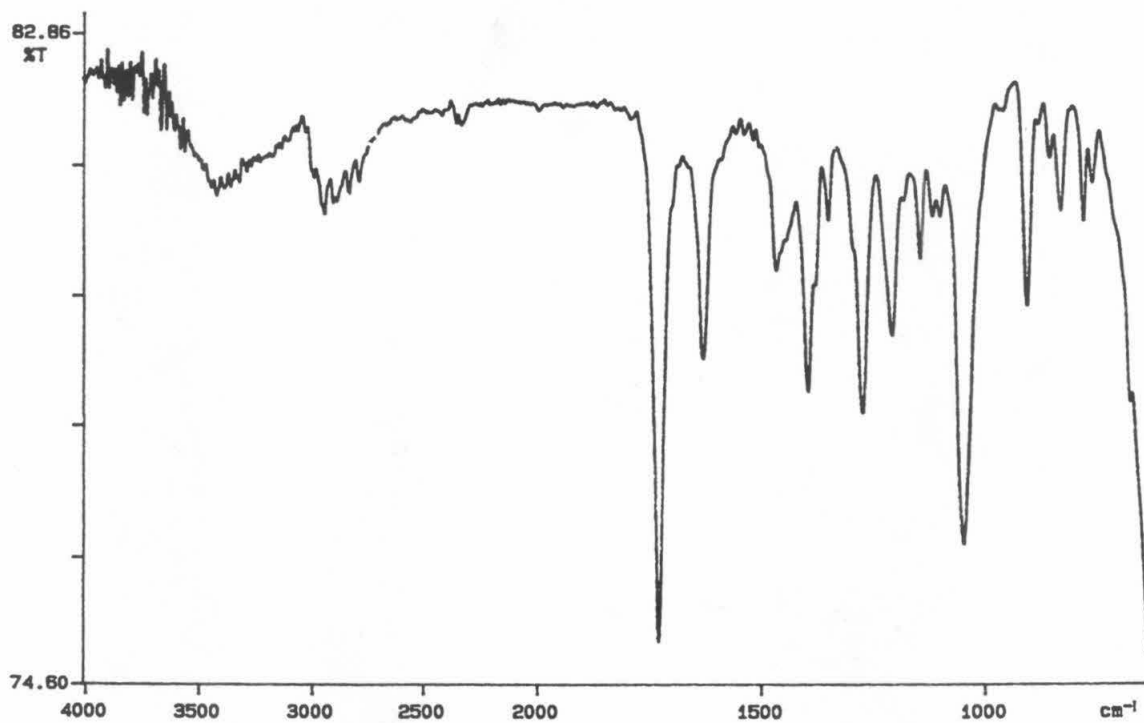
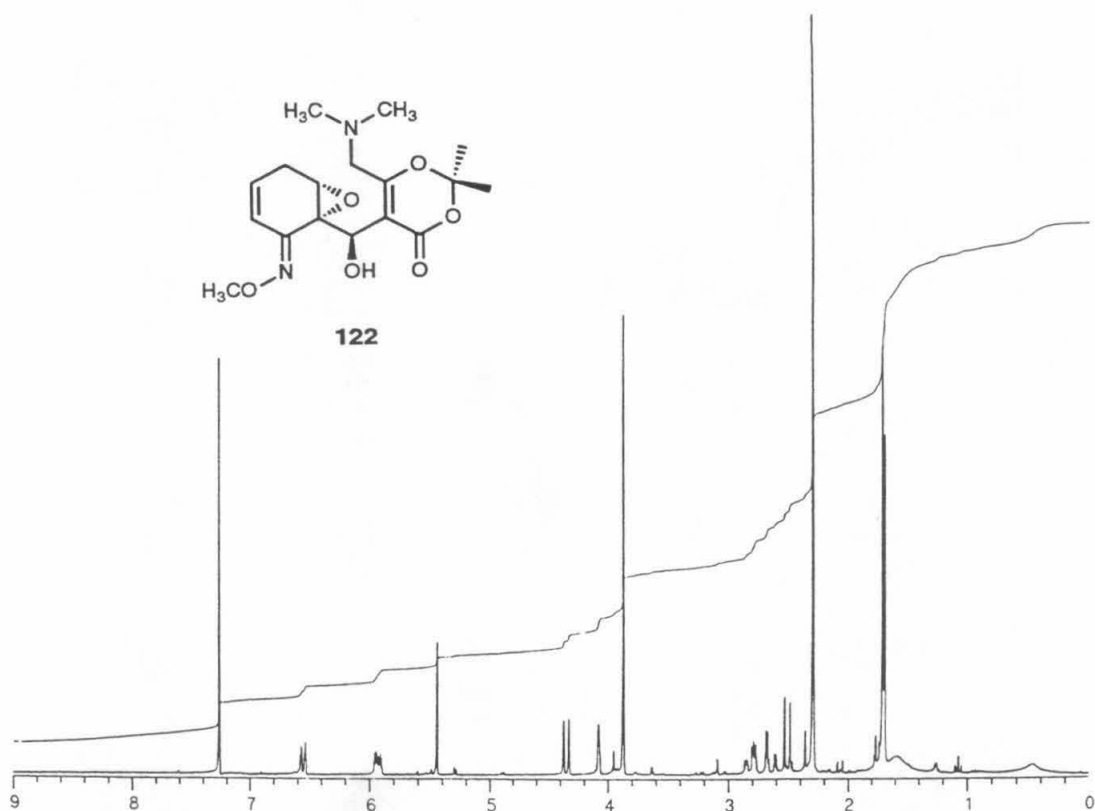


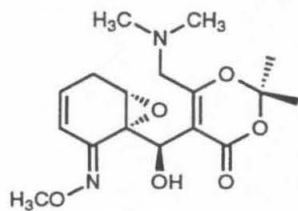
**120****121**



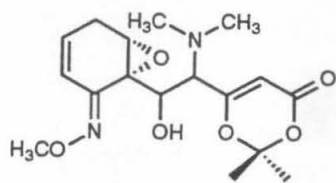
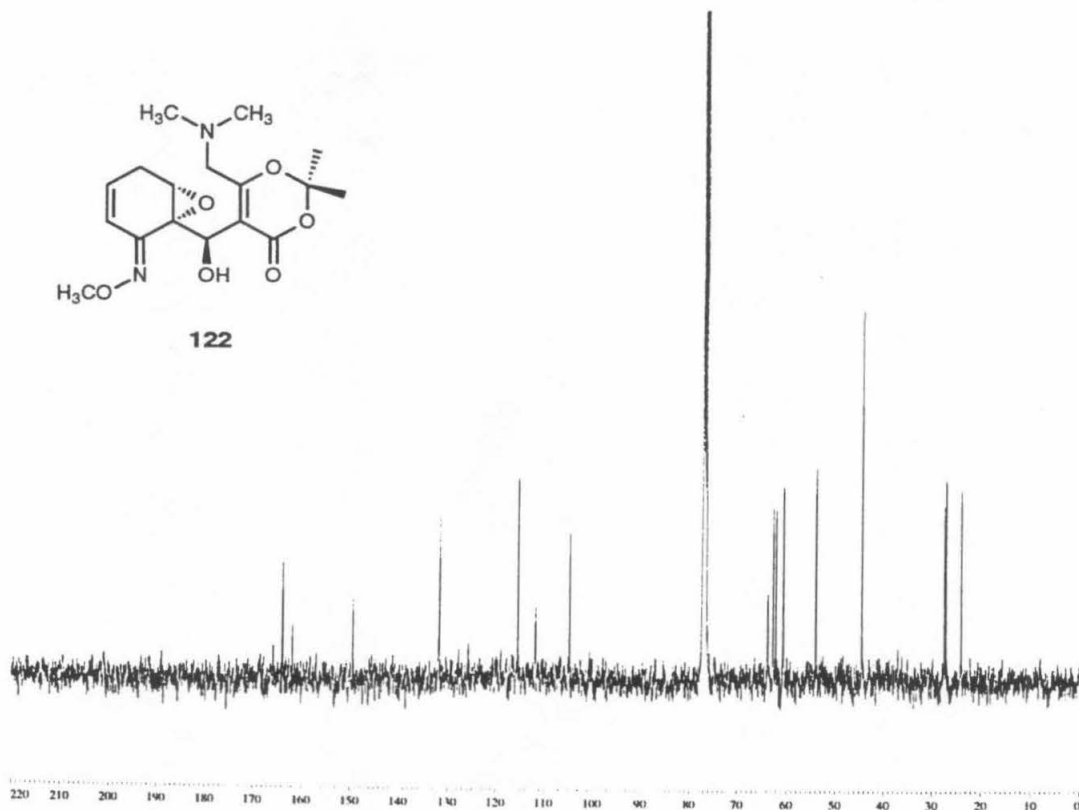


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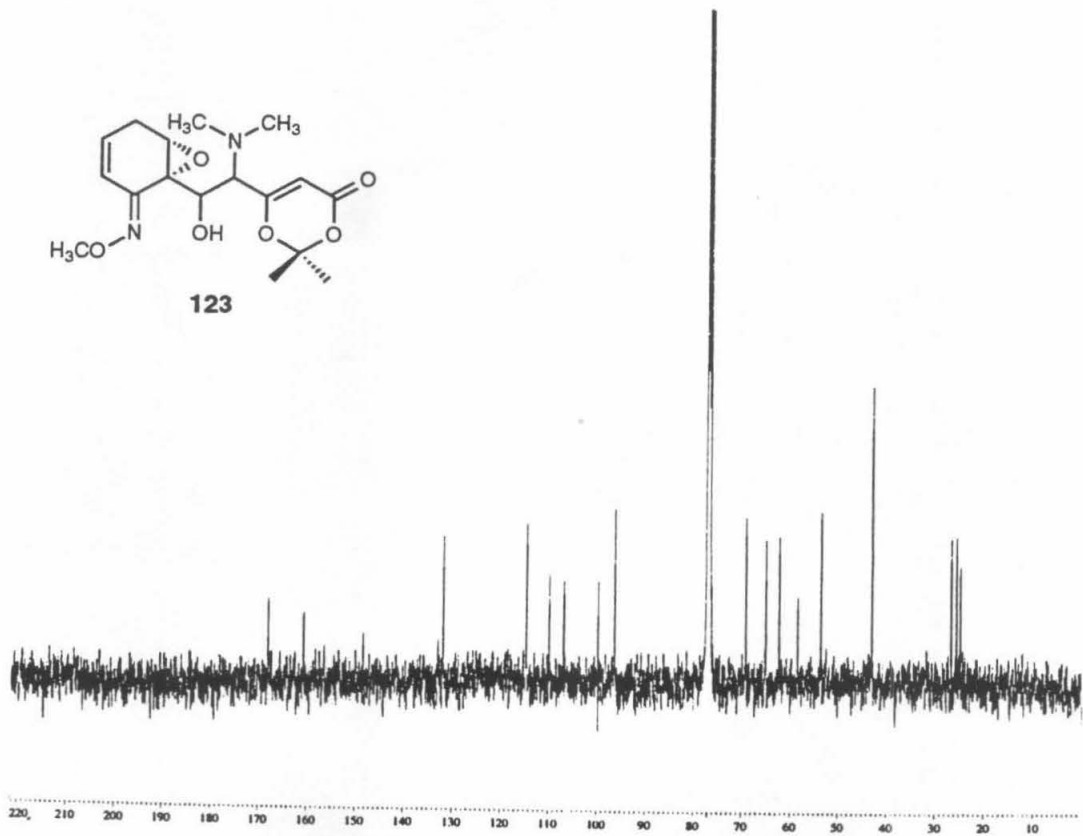


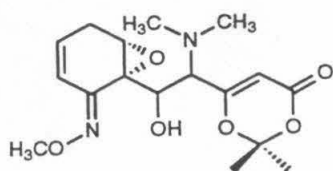
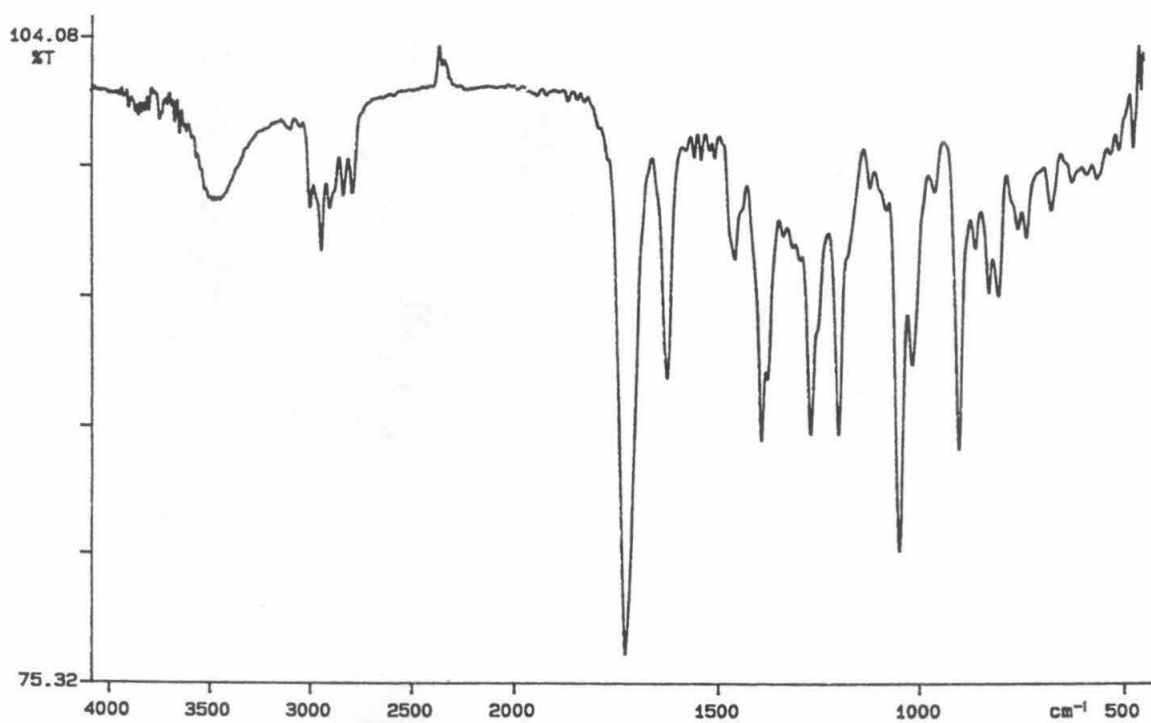
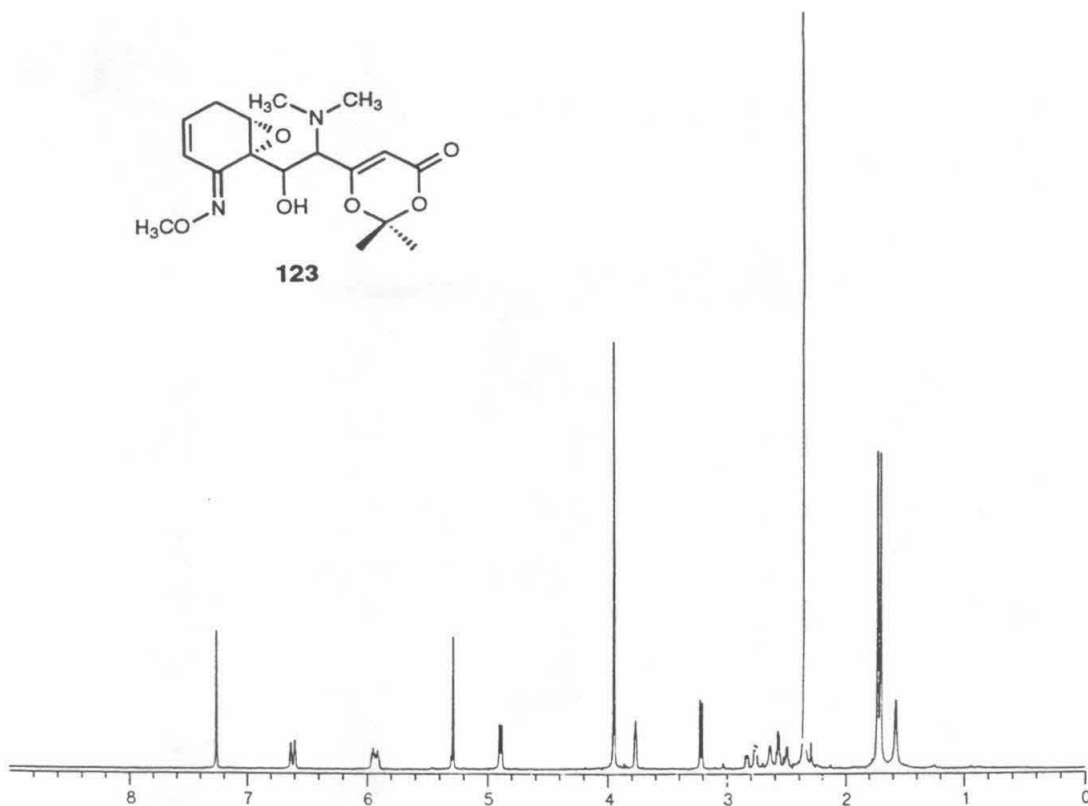


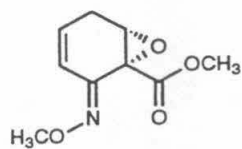
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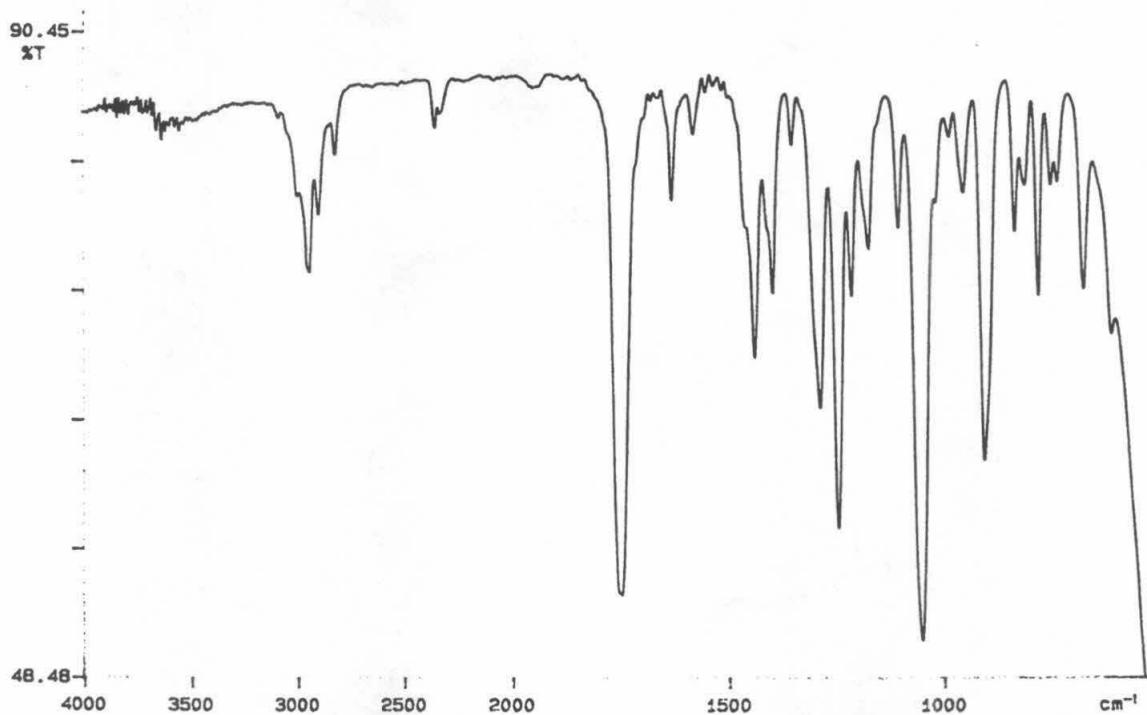
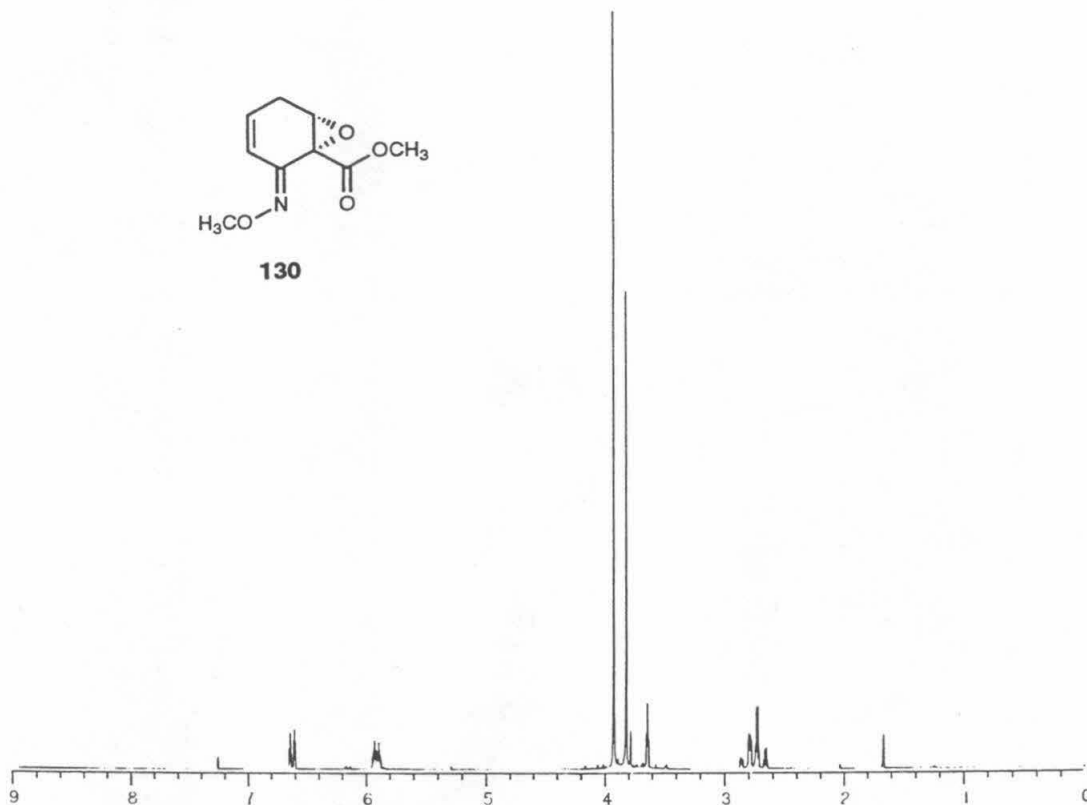
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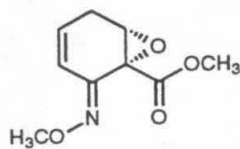
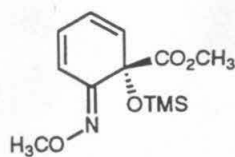
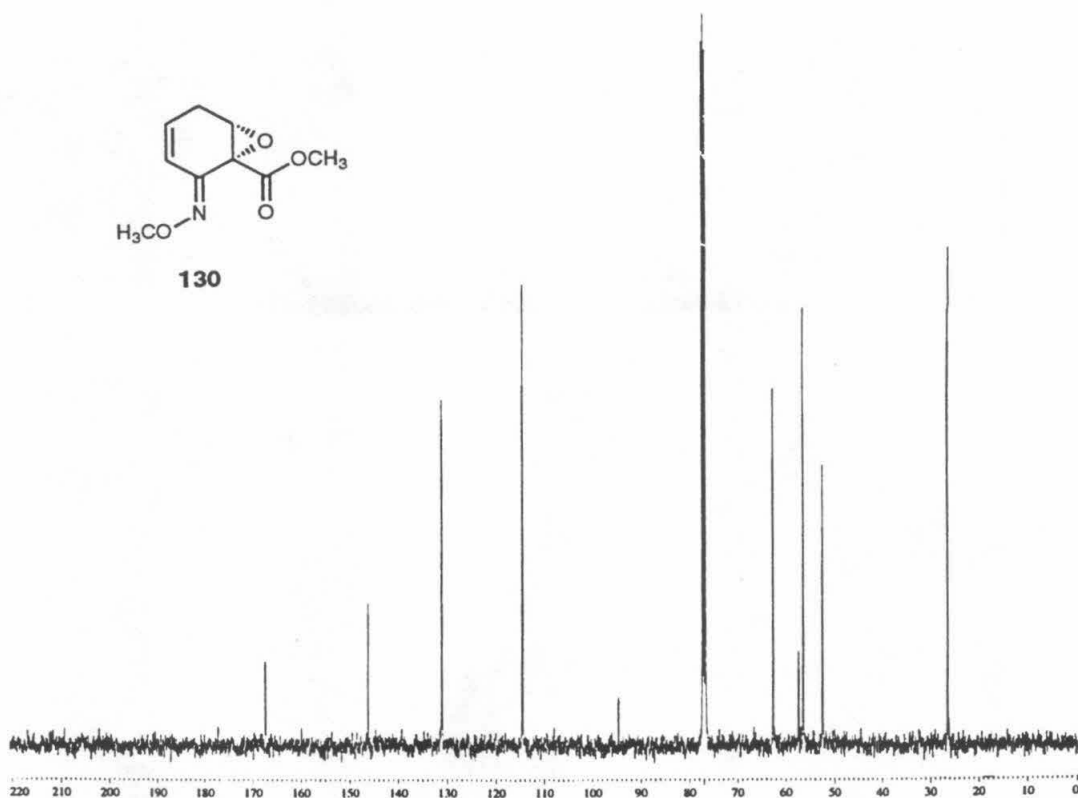
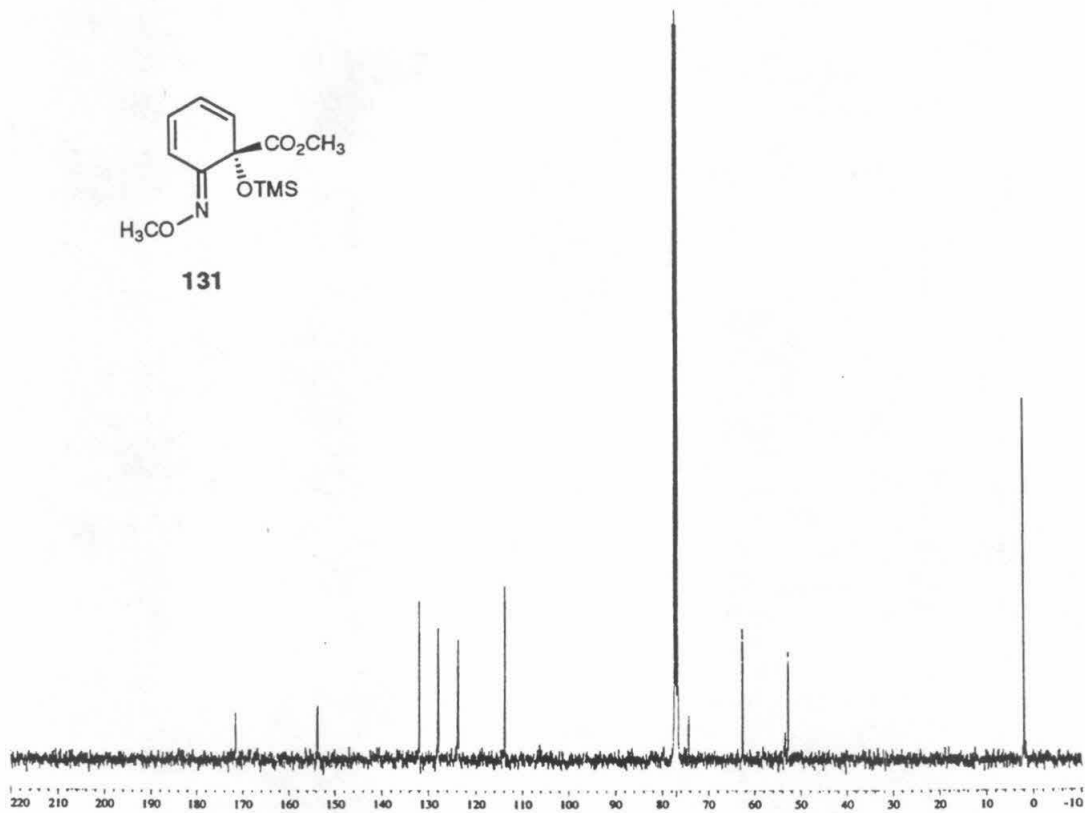


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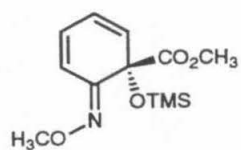
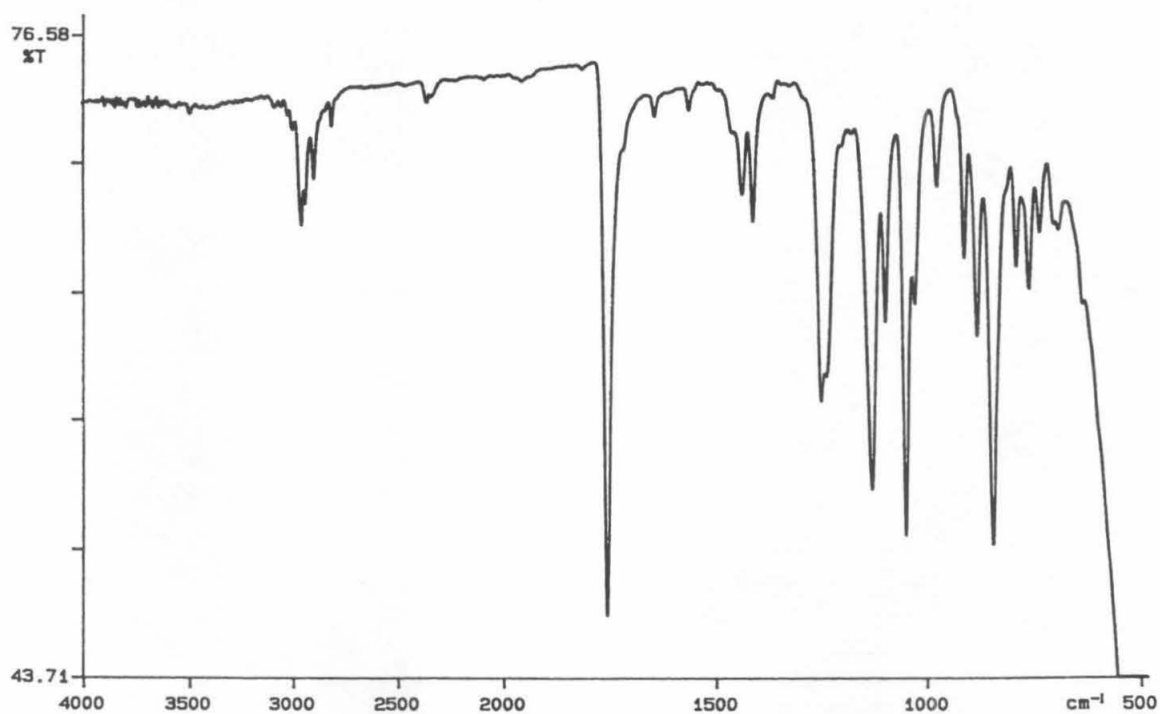
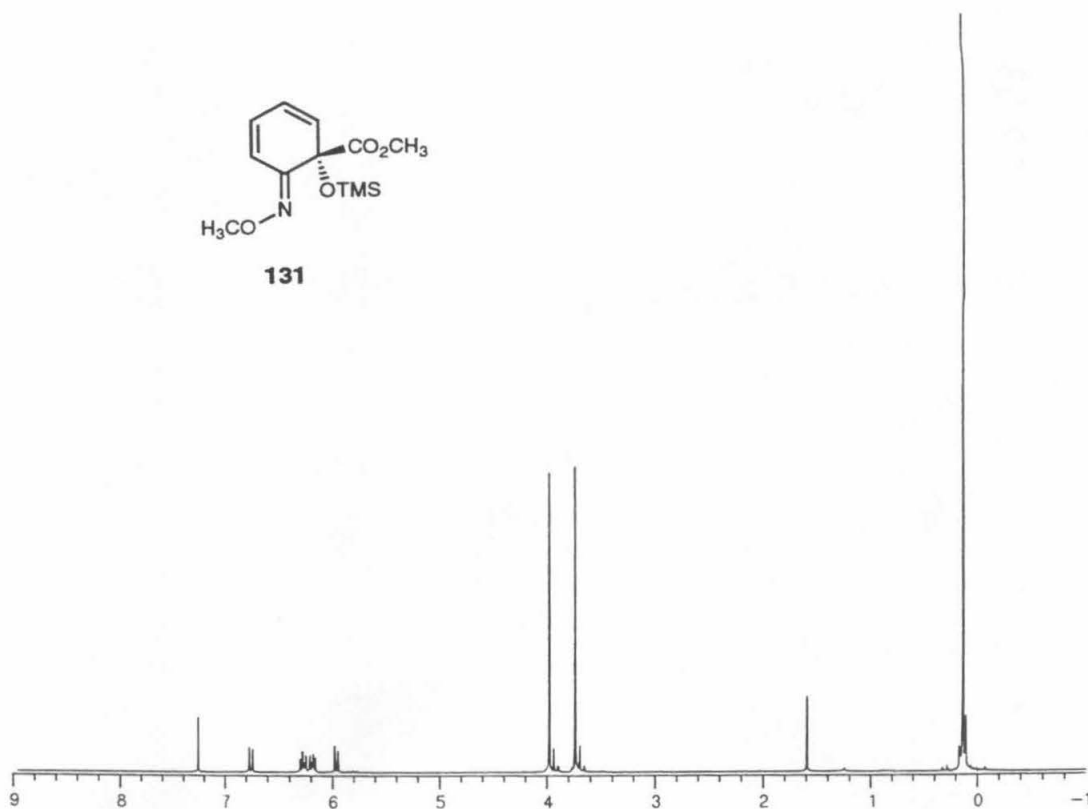


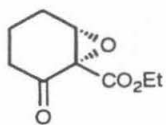
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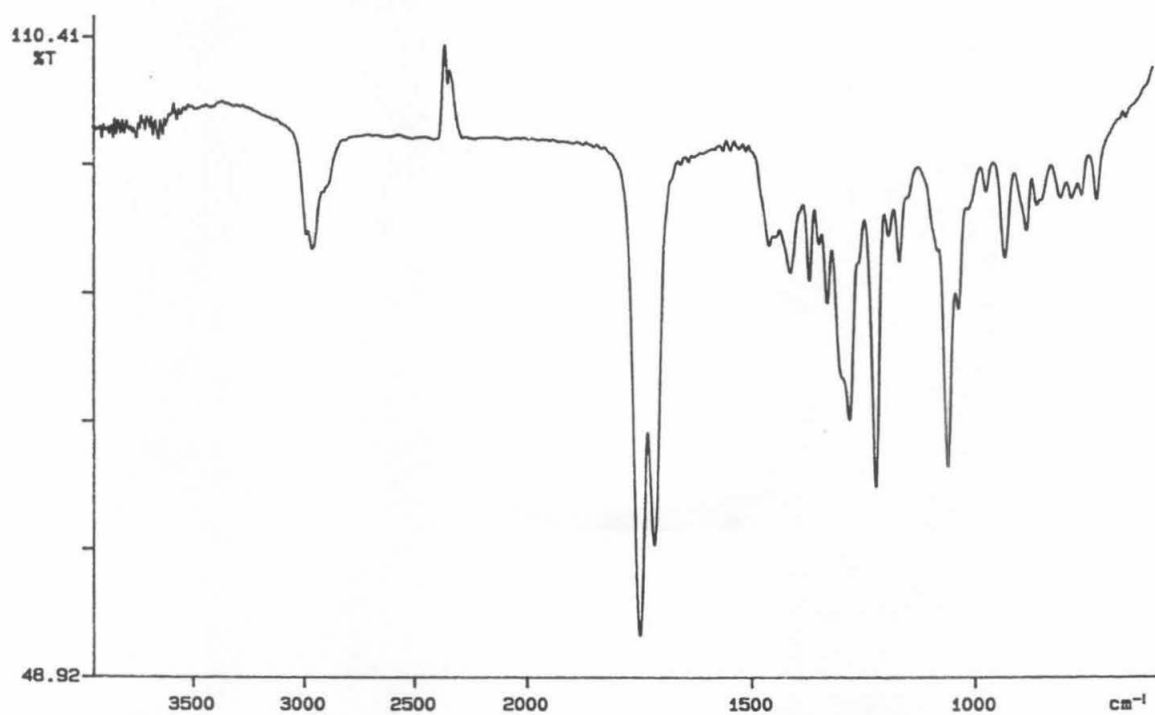
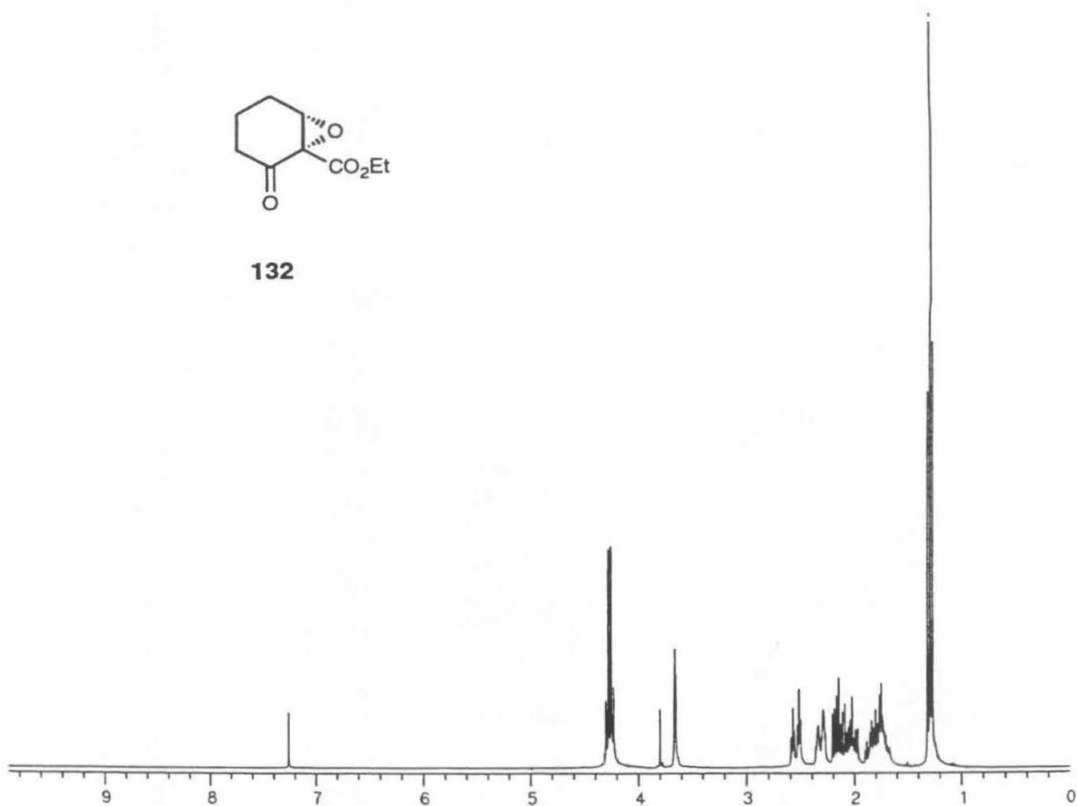
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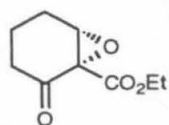


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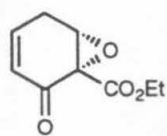
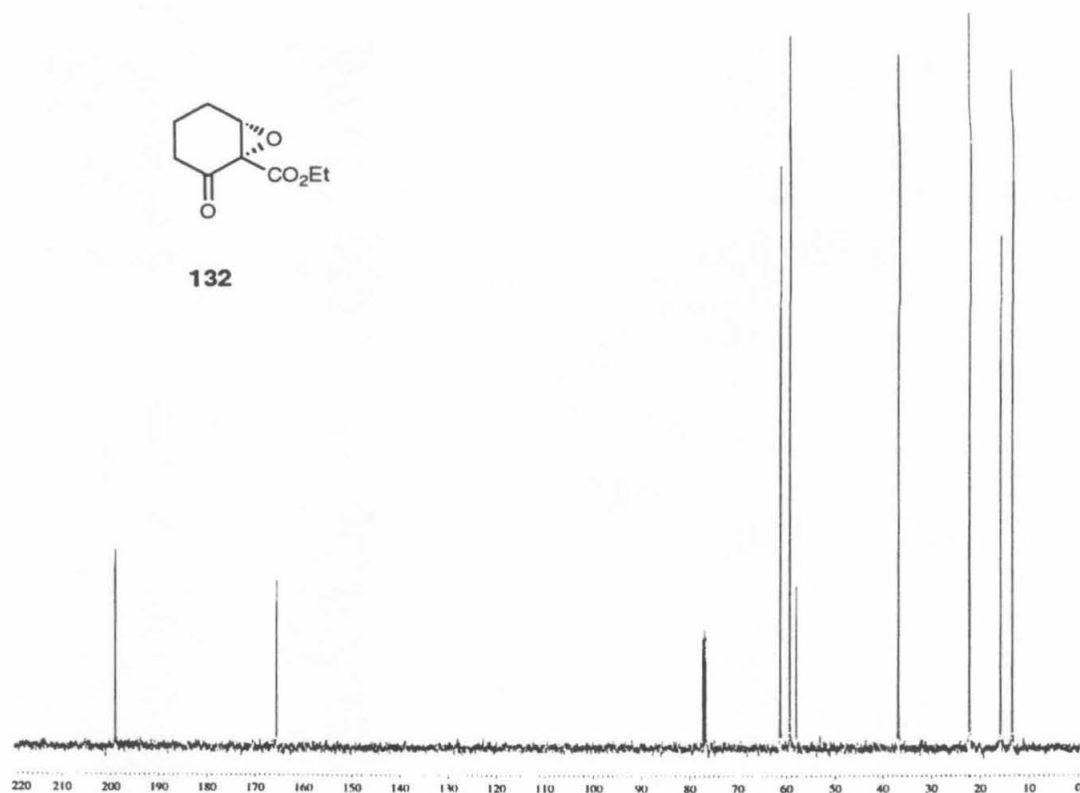


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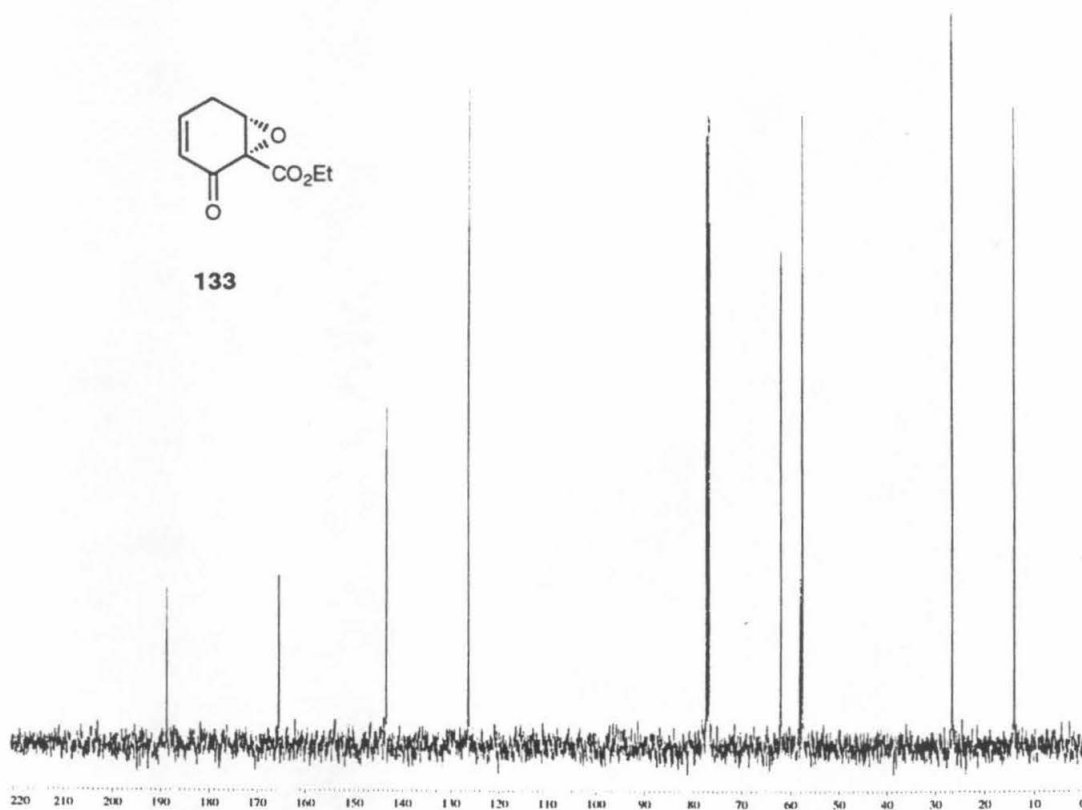


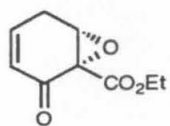
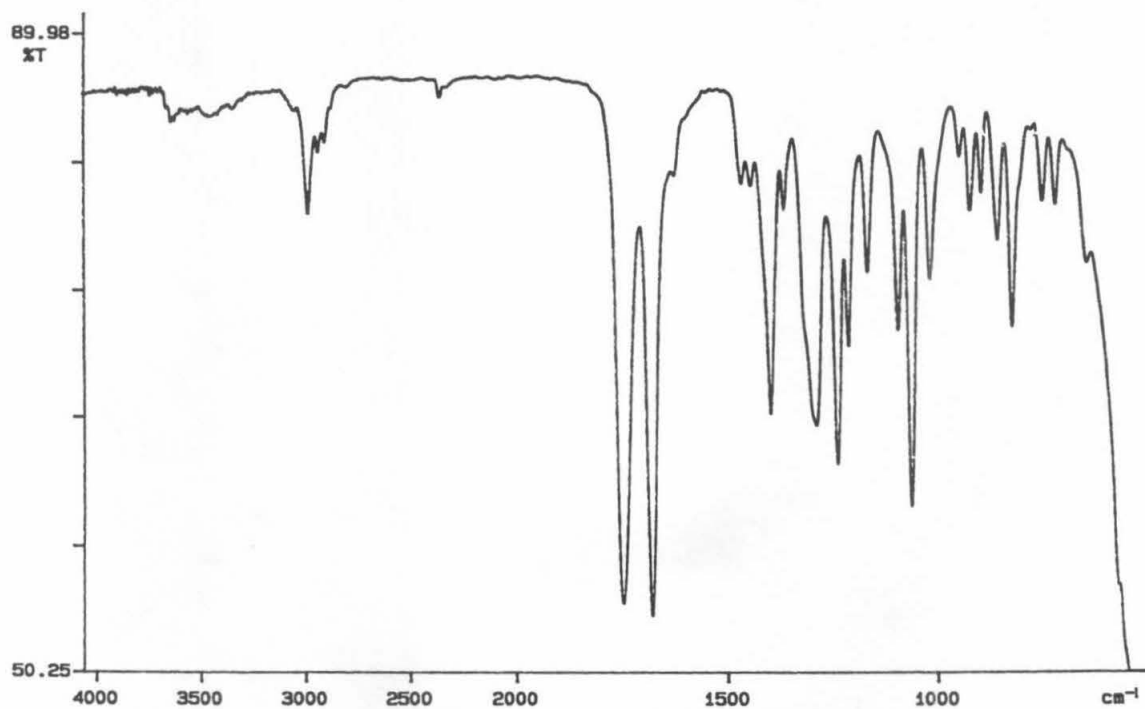
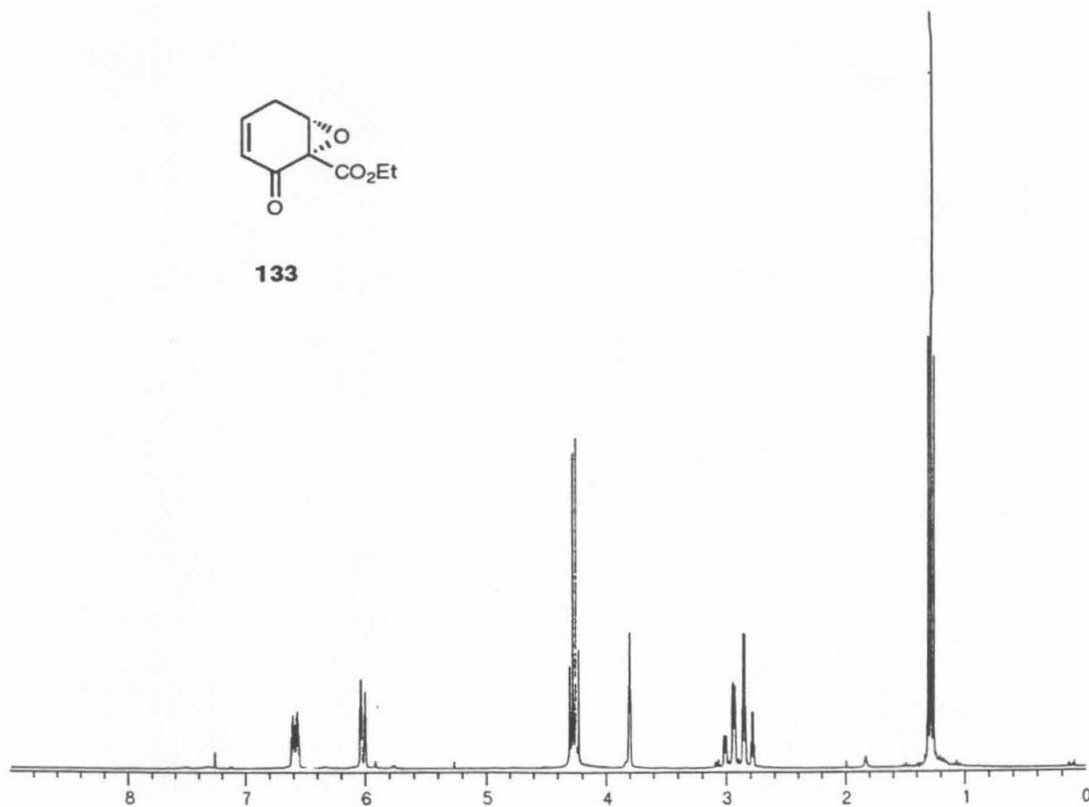


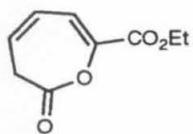
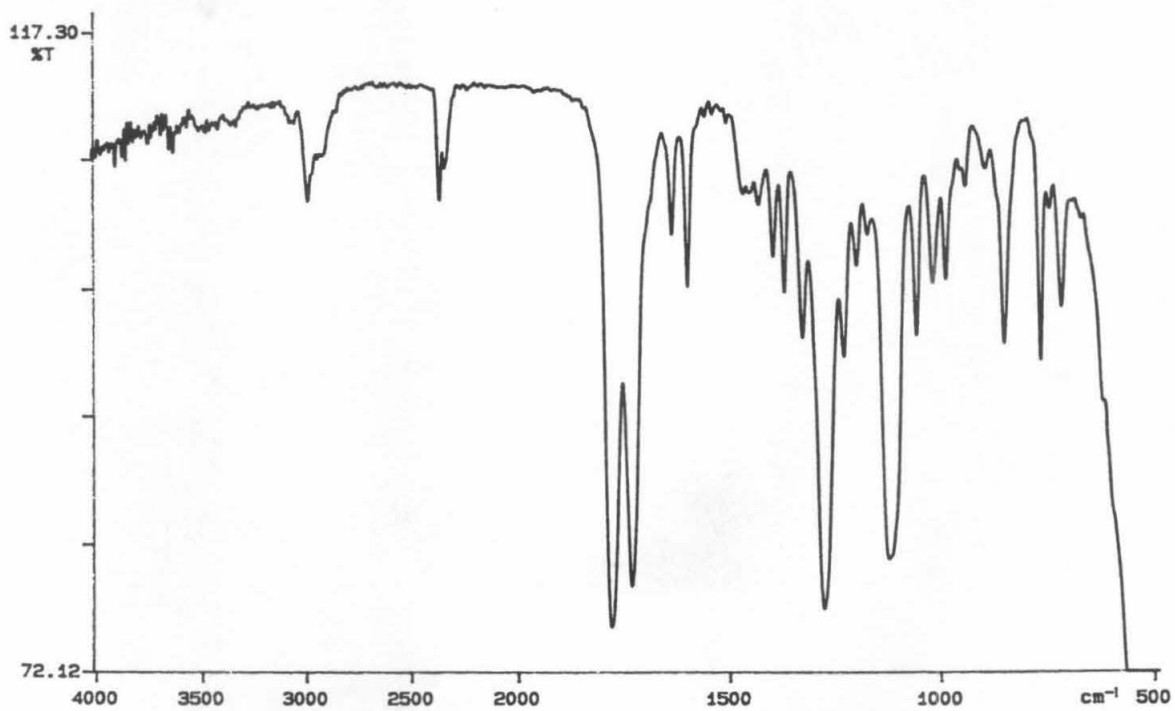
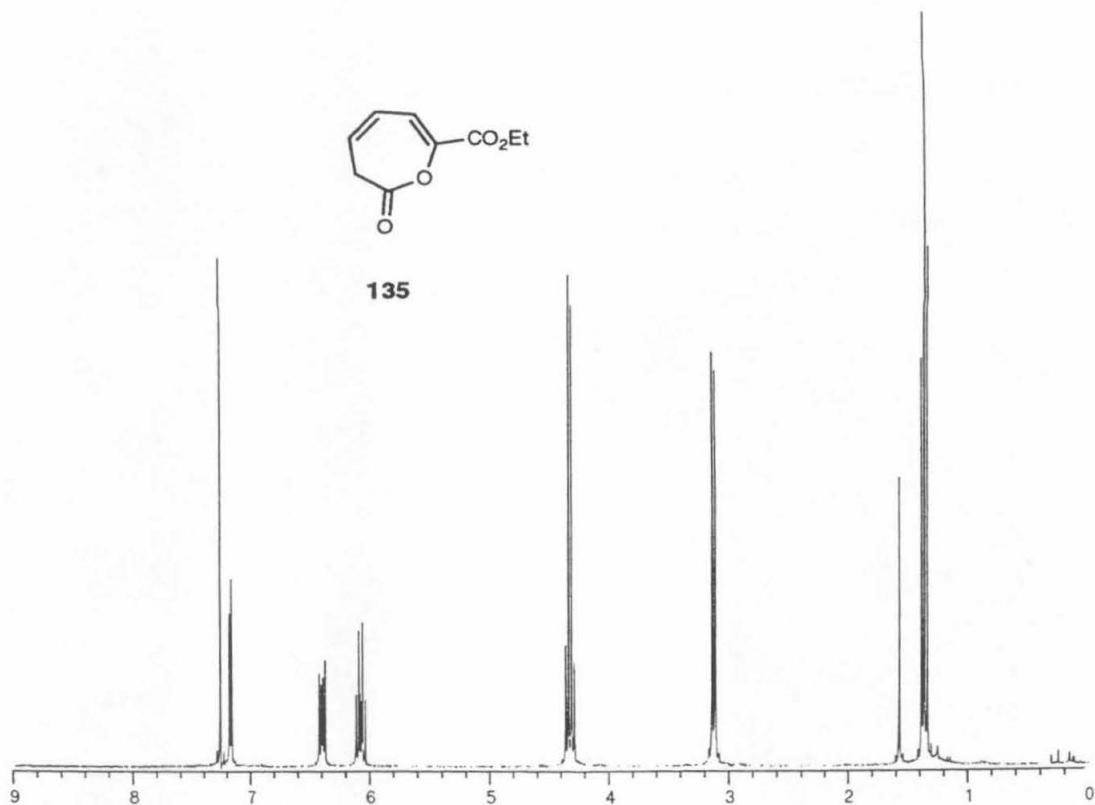
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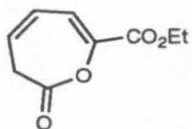


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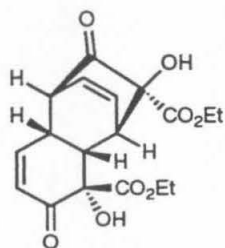
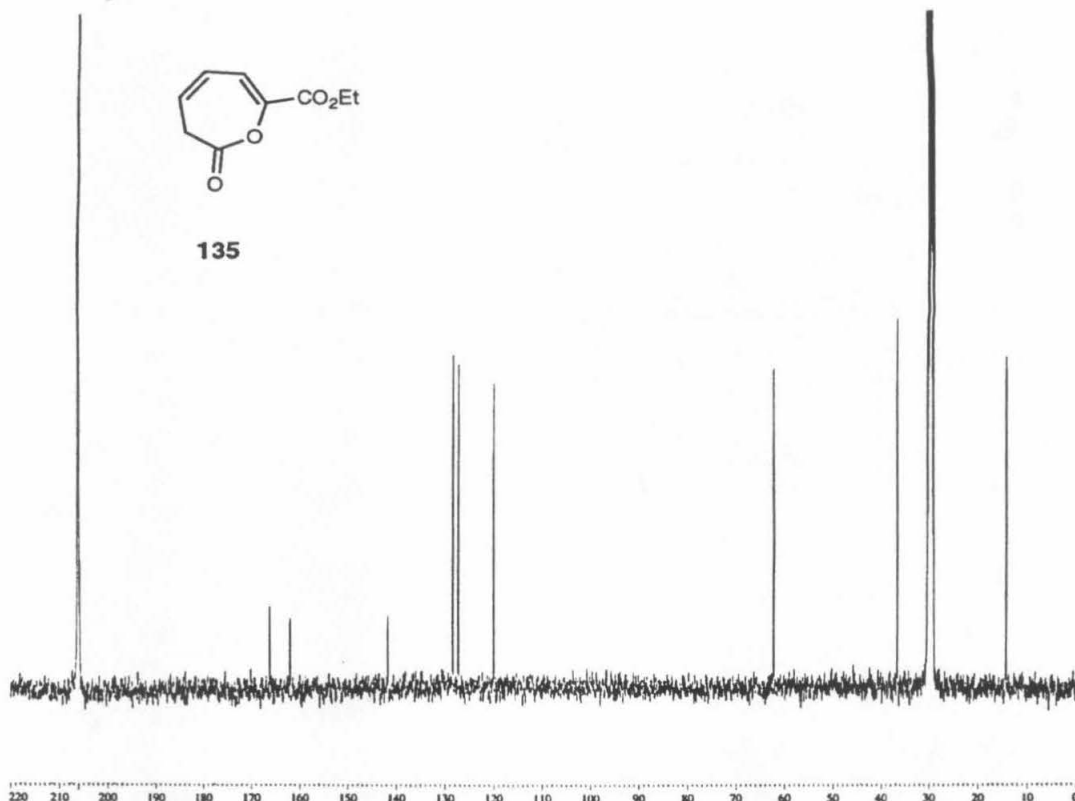


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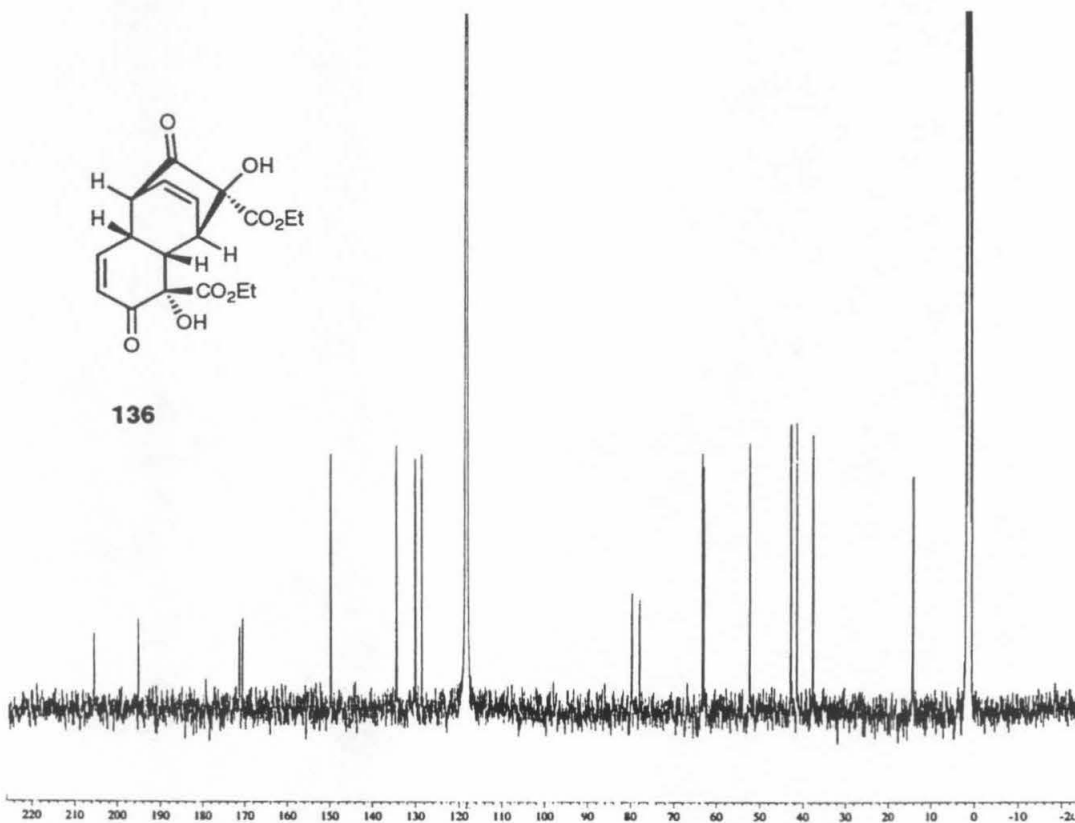
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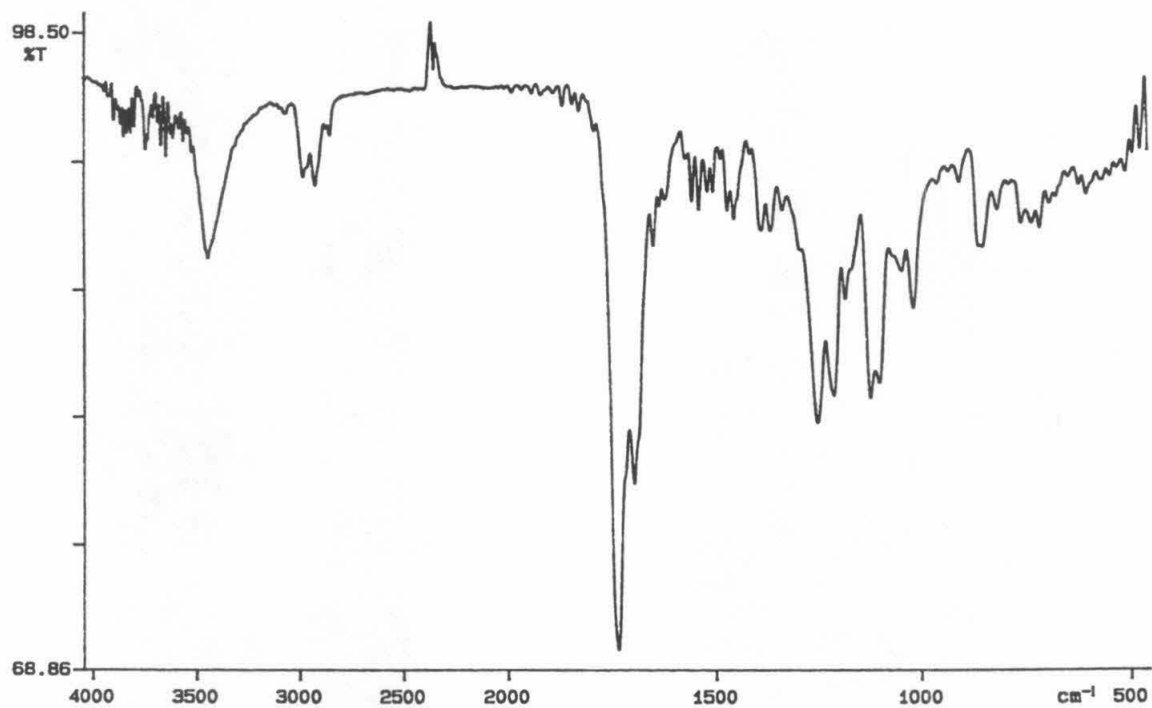
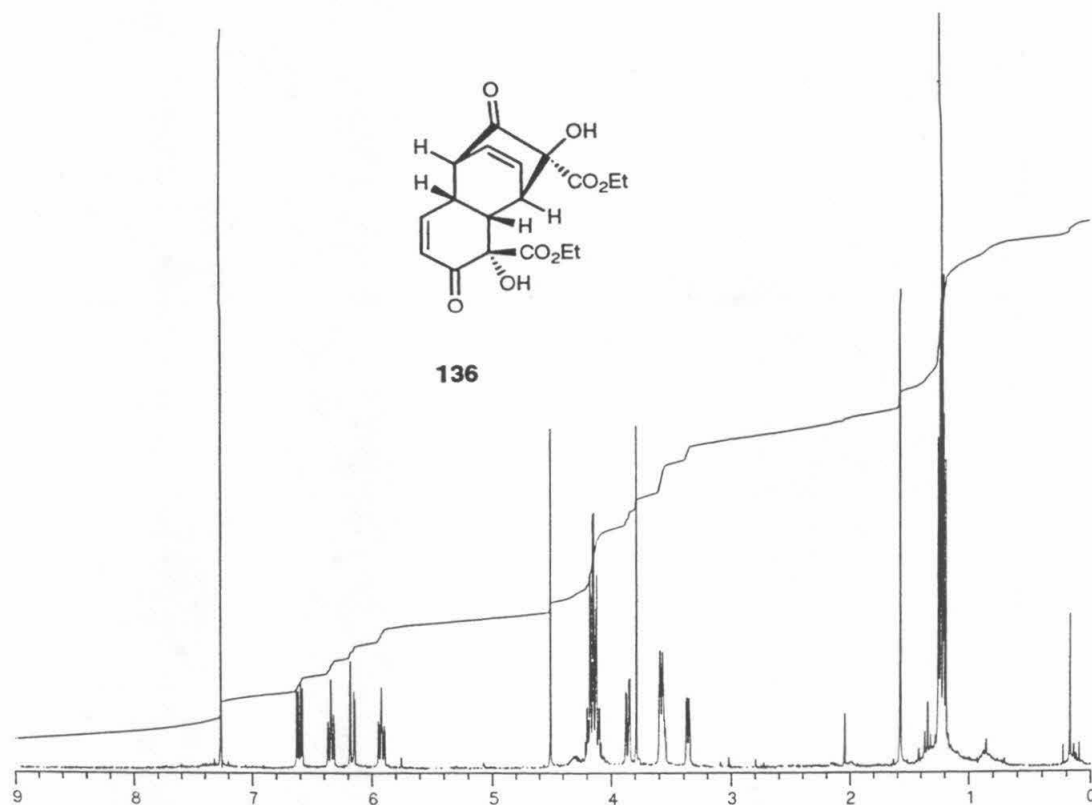


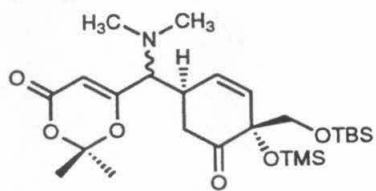
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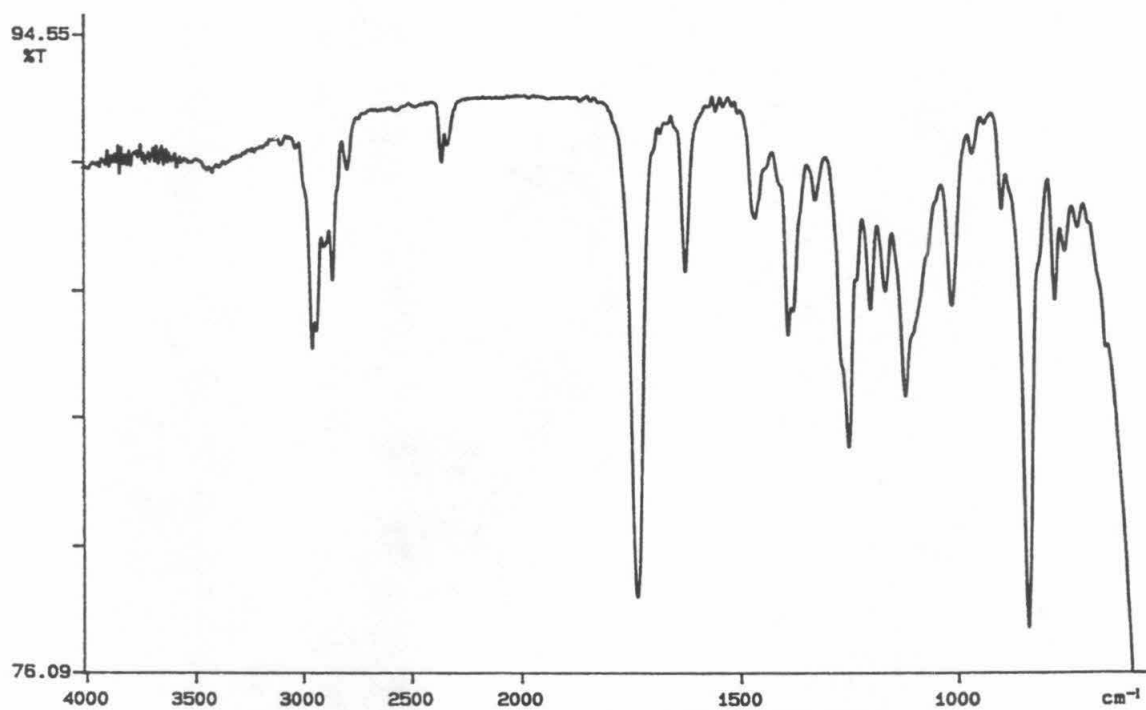
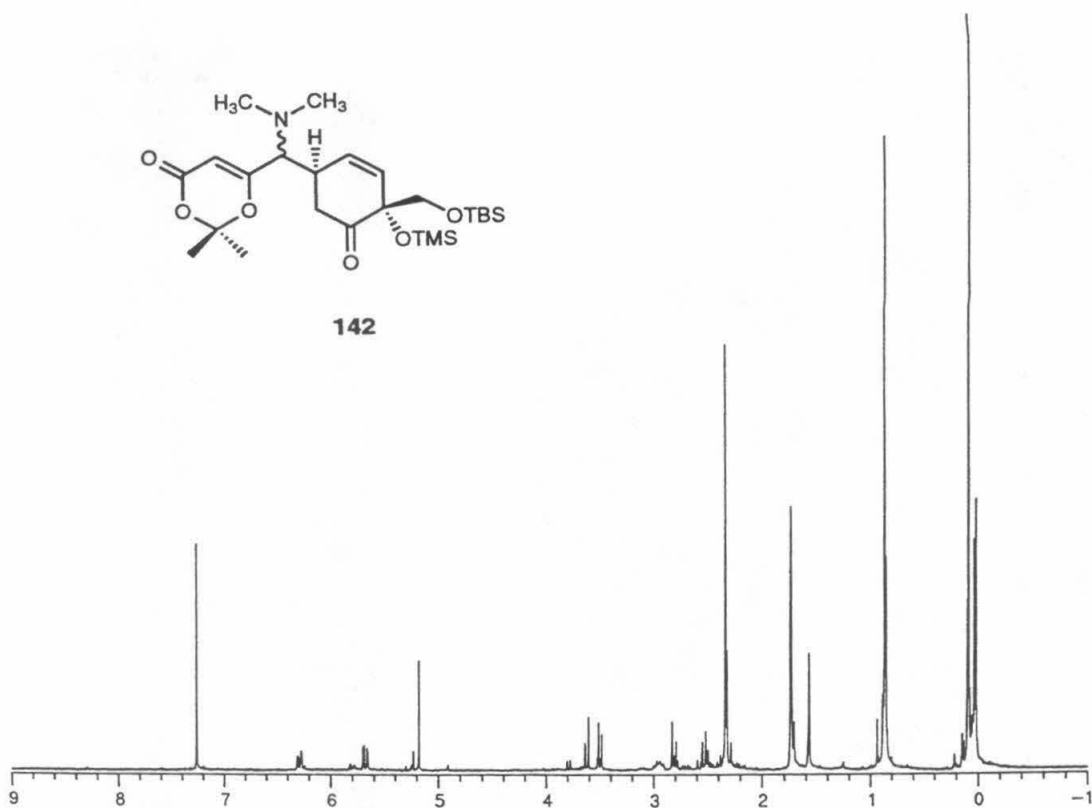
136



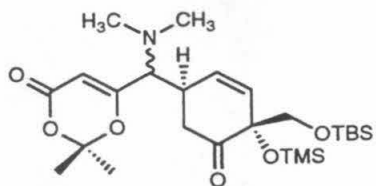
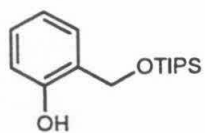
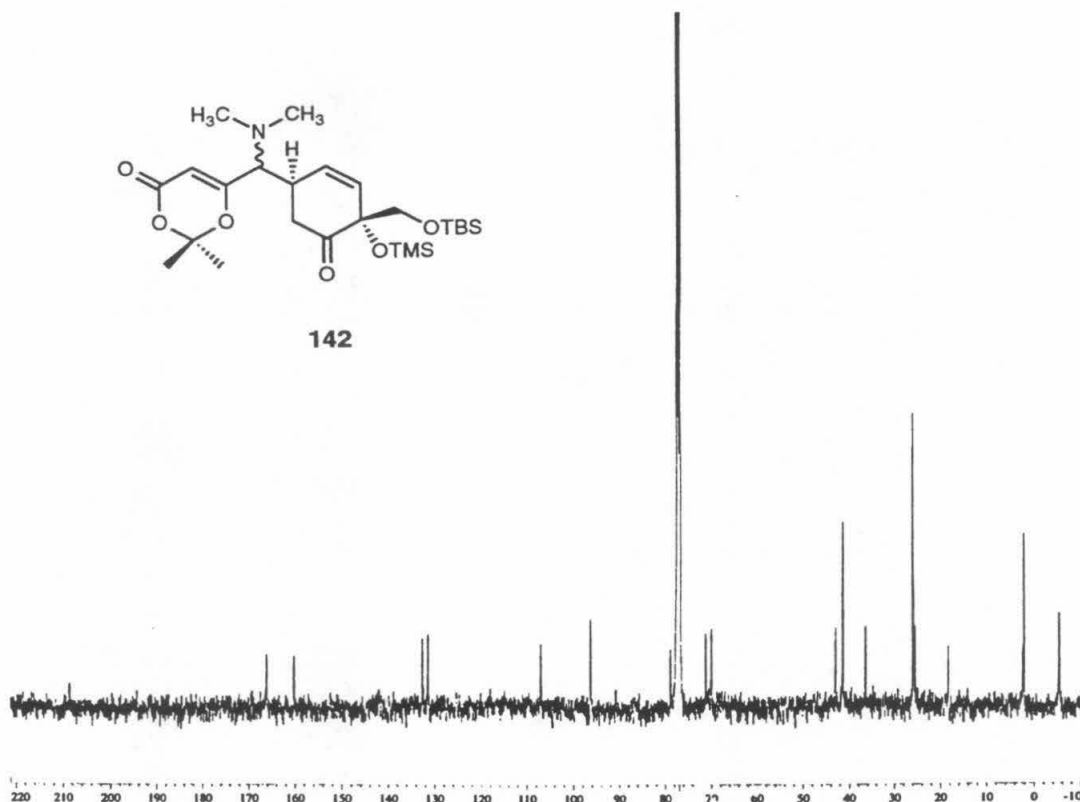
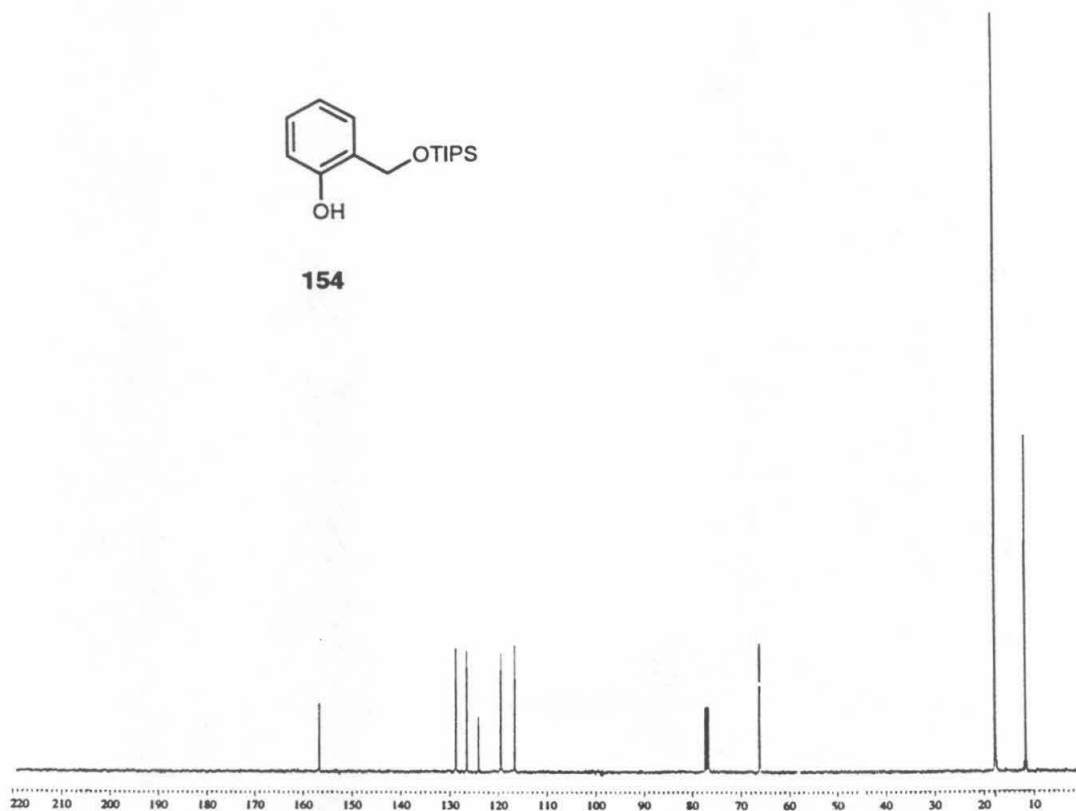


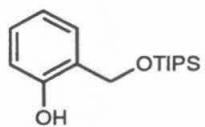
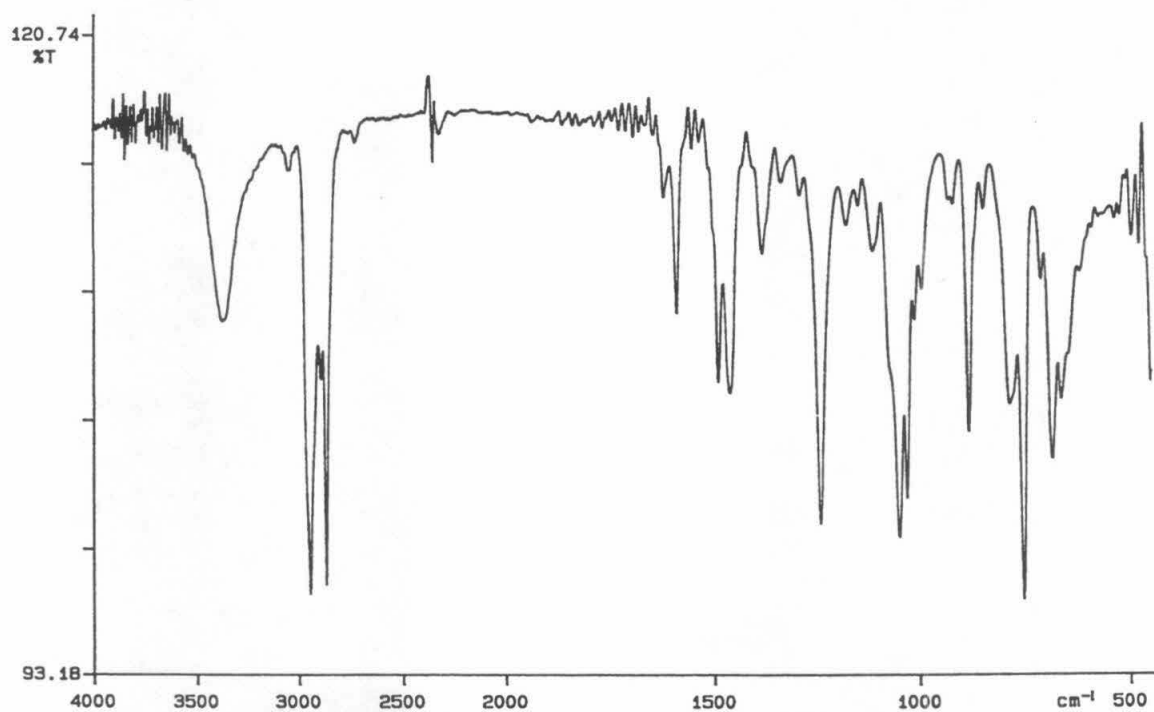
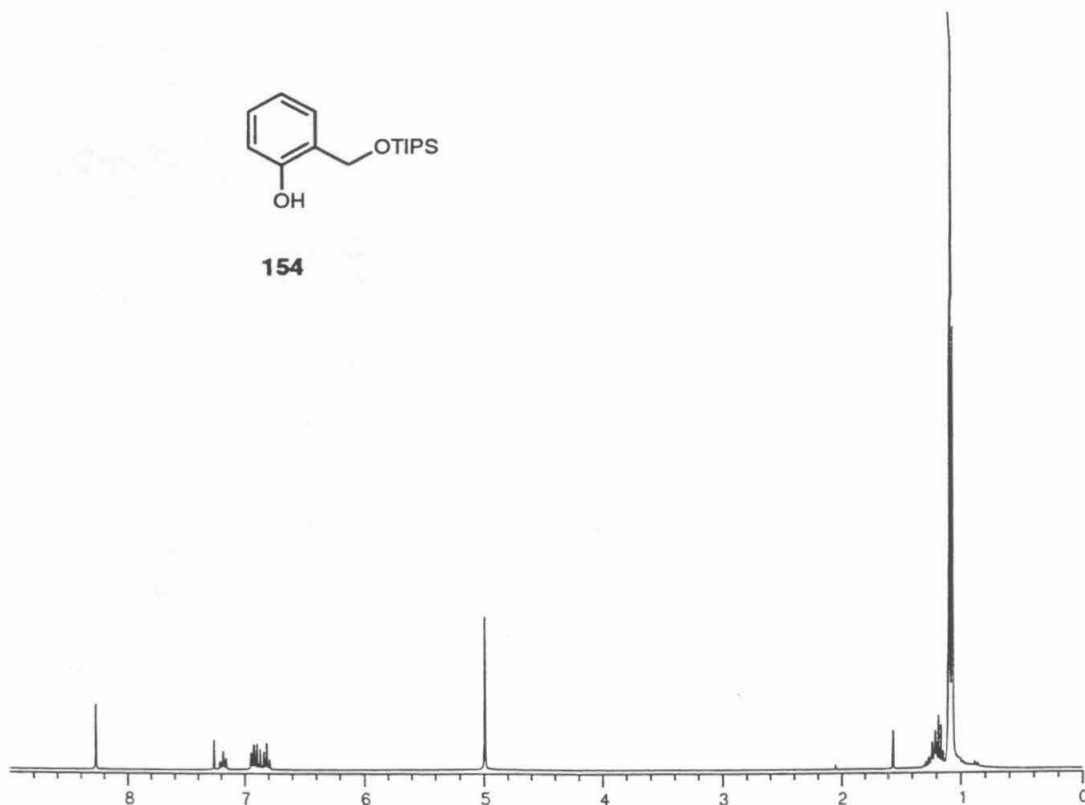


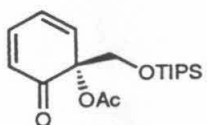
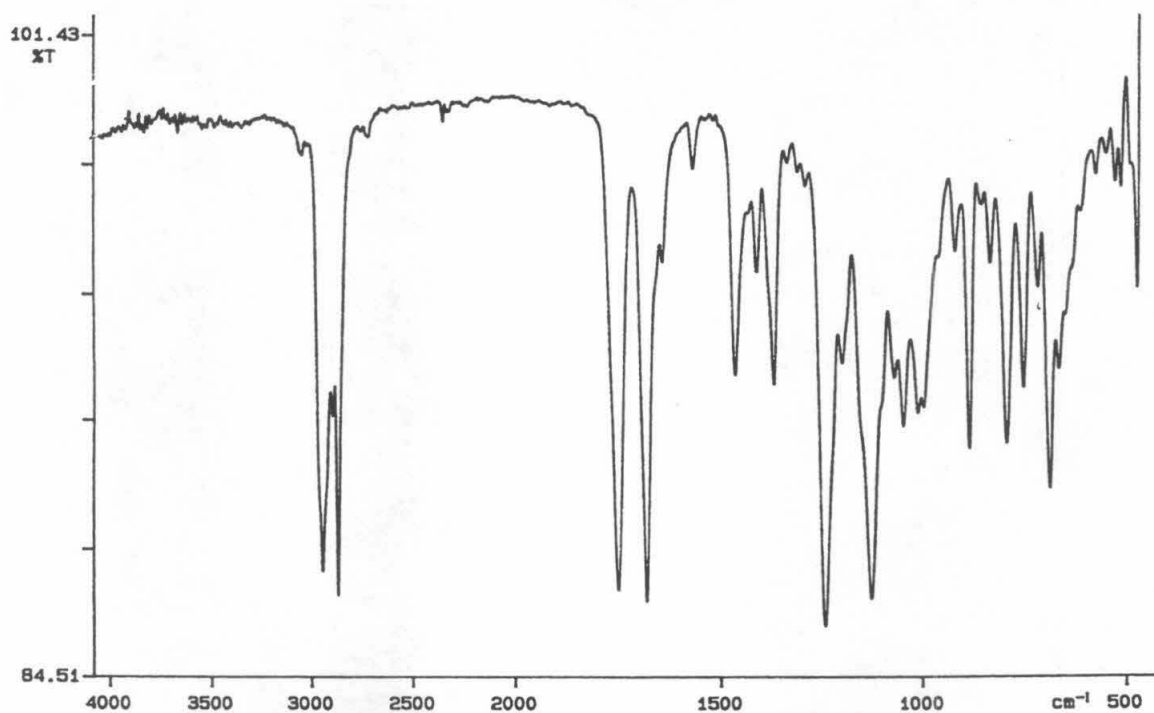
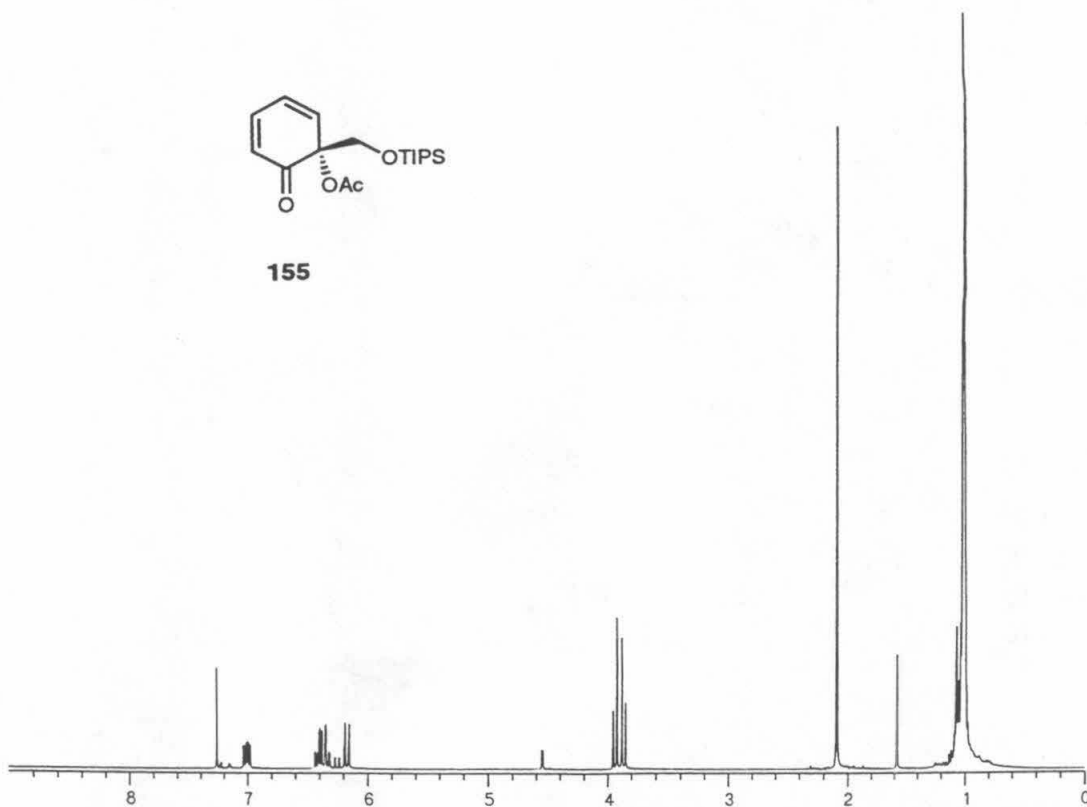
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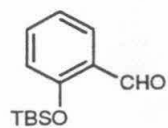
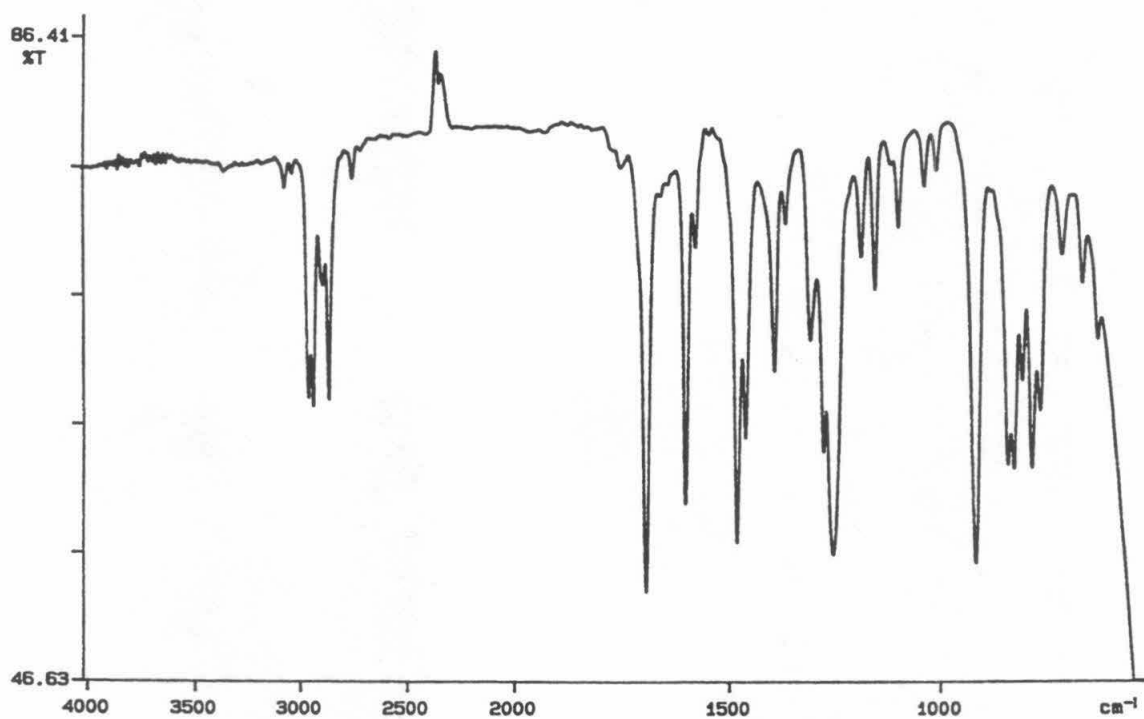
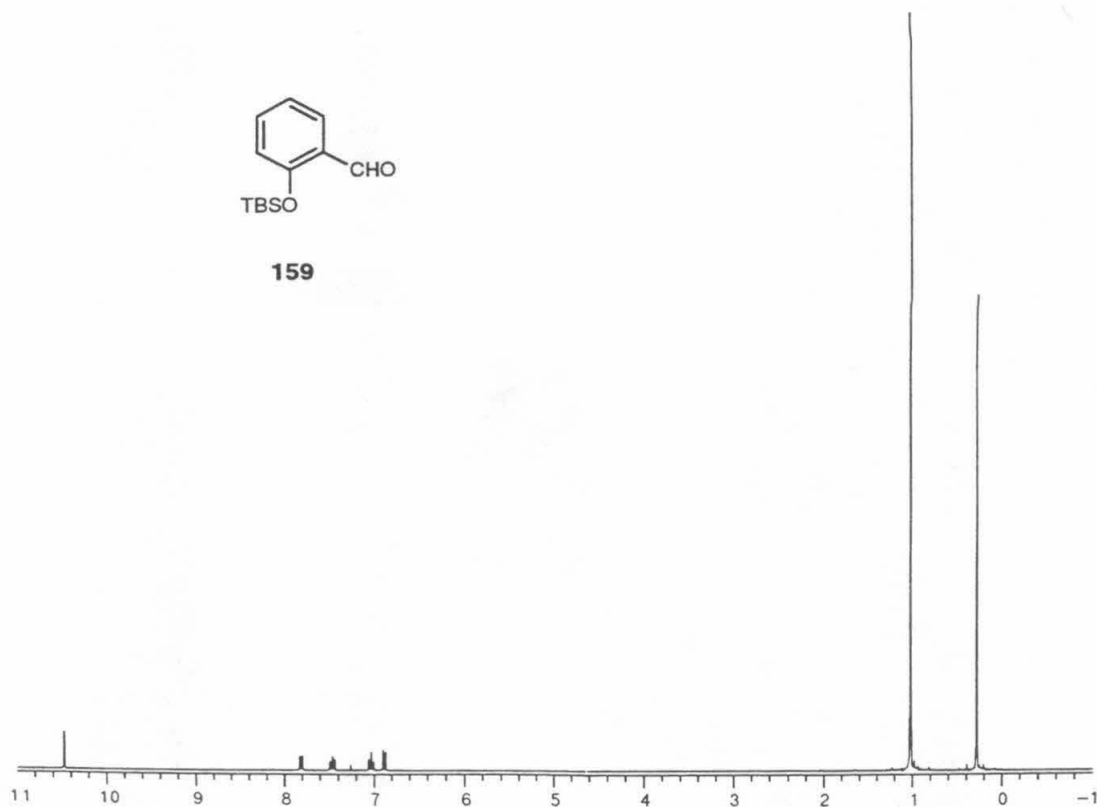


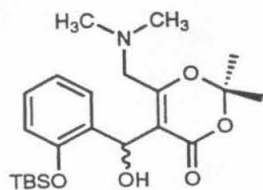
**142****154**

**154**

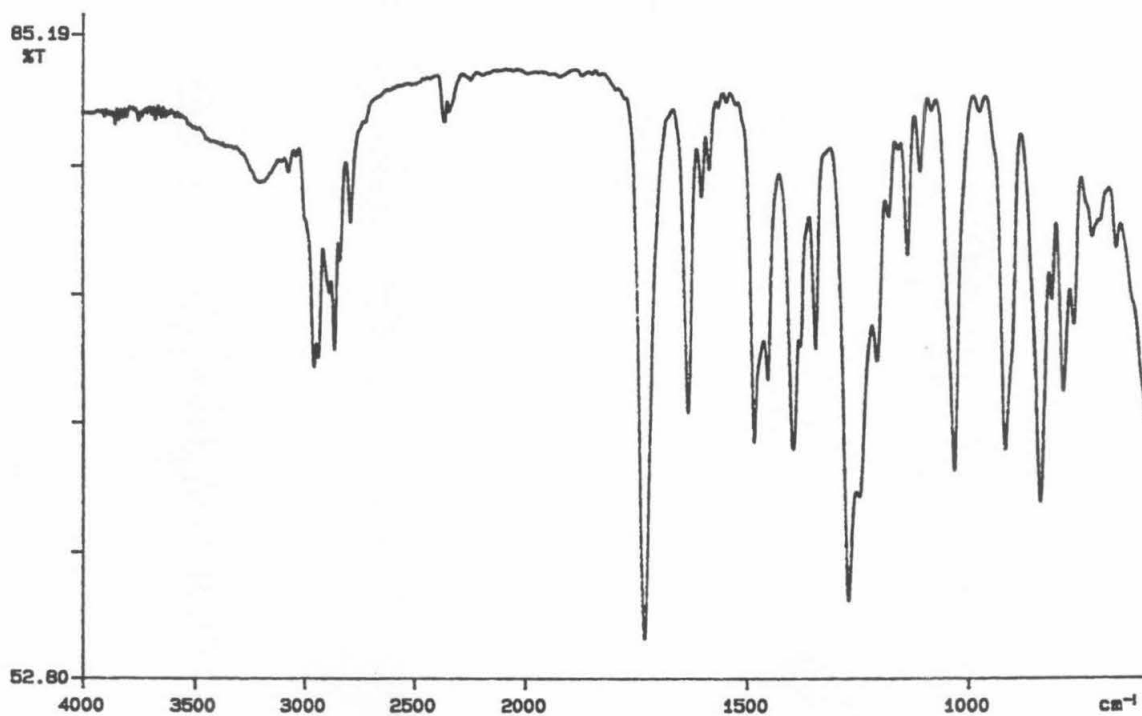
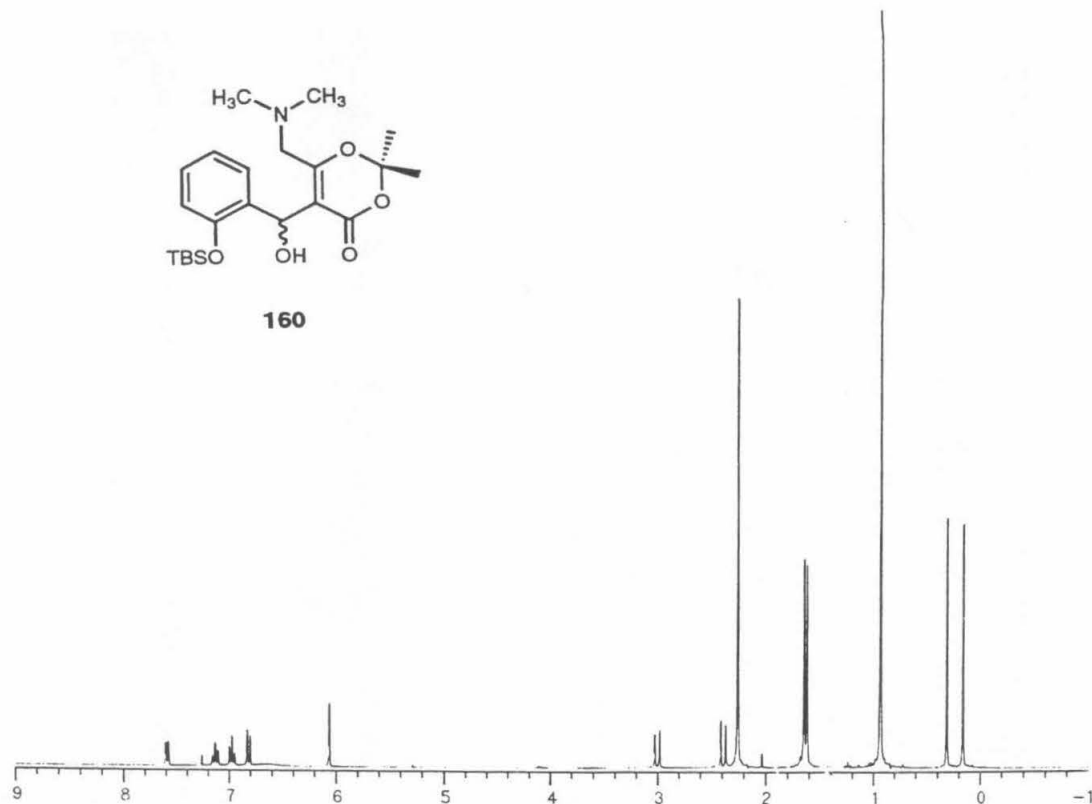
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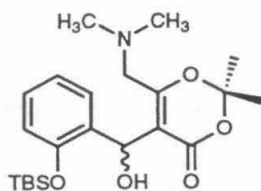
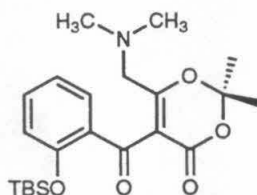
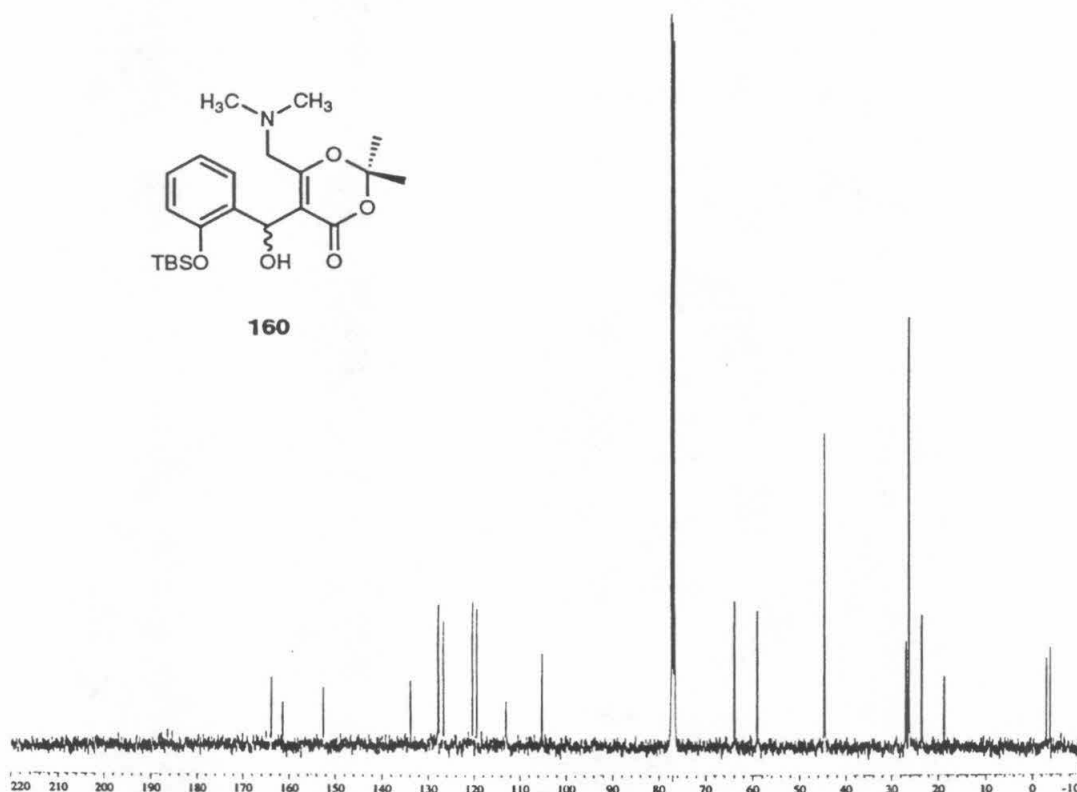
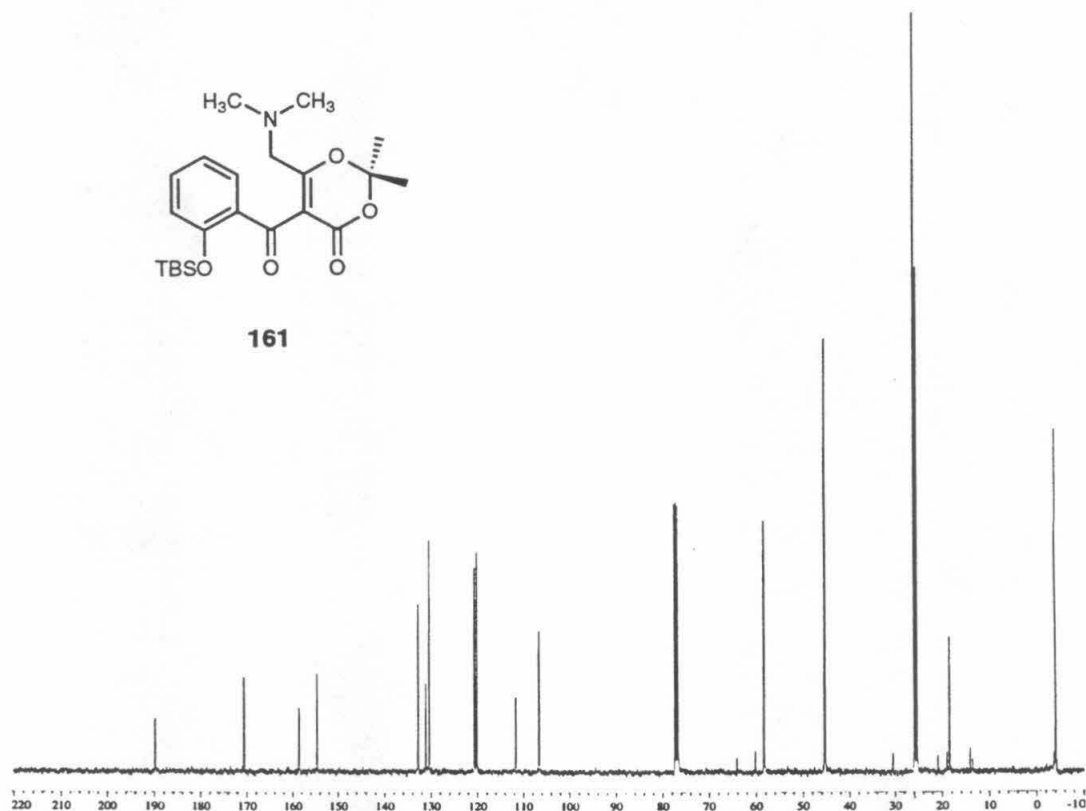


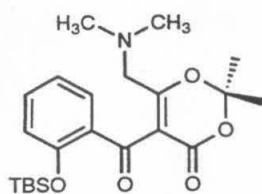
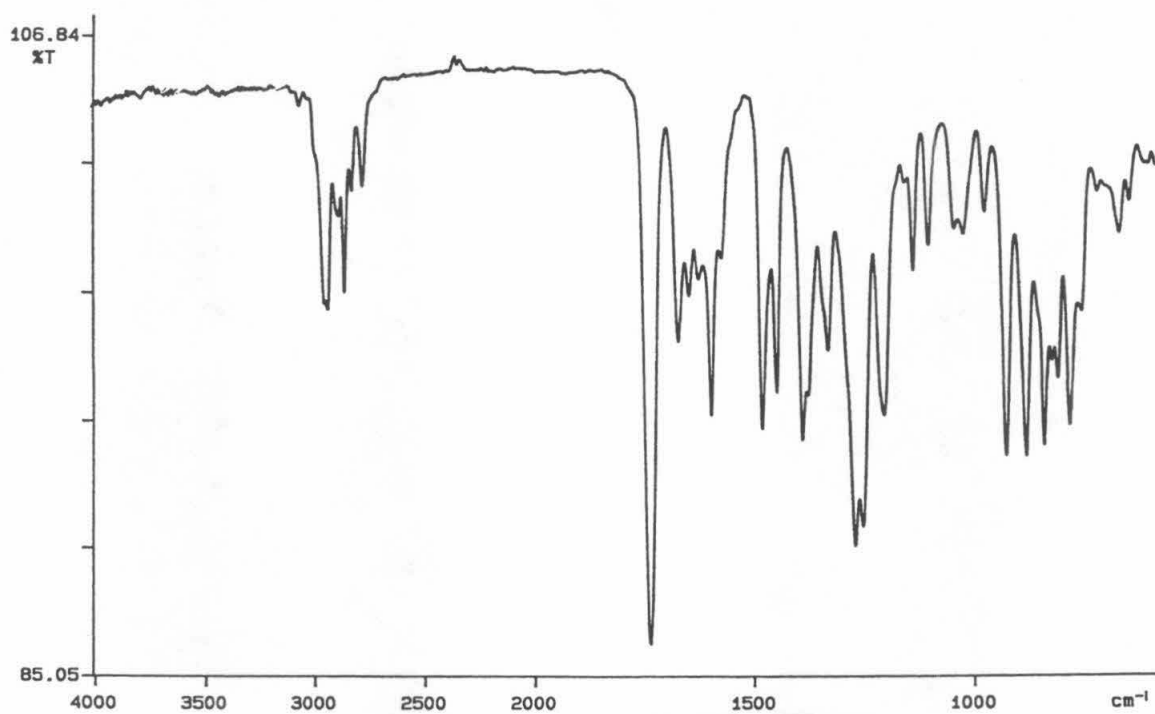
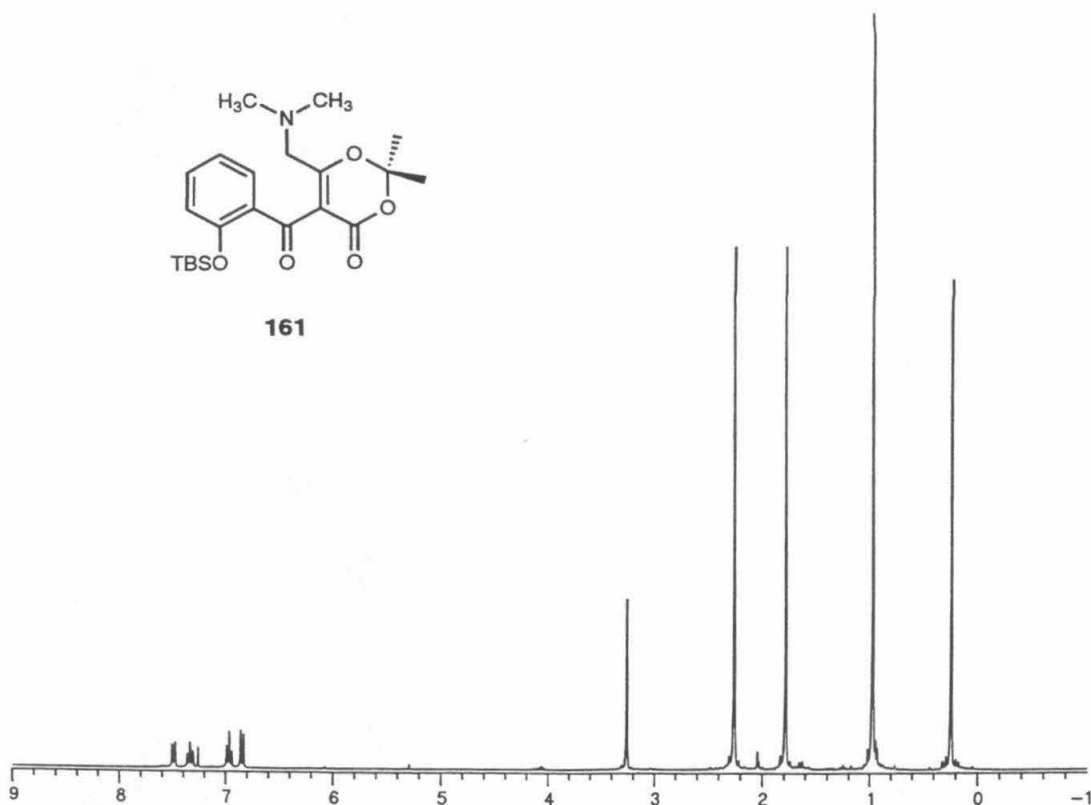
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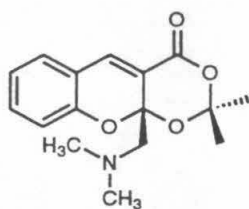
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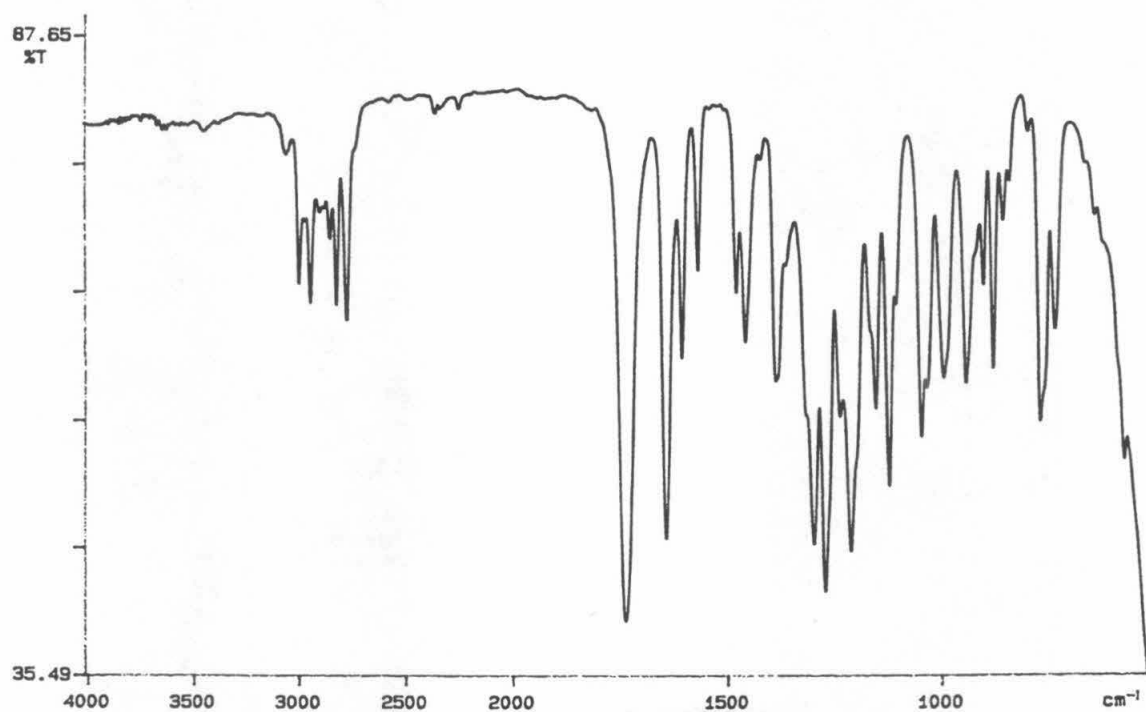
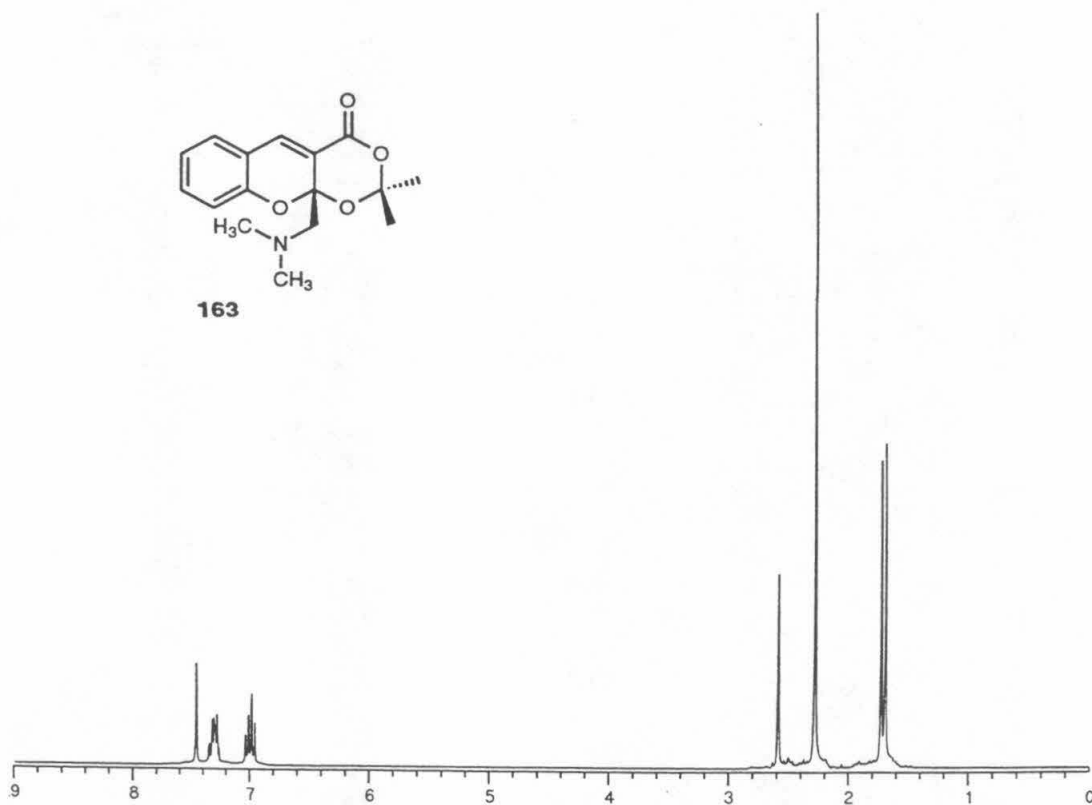
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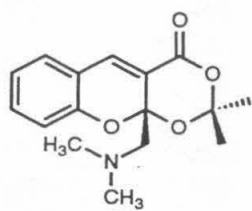
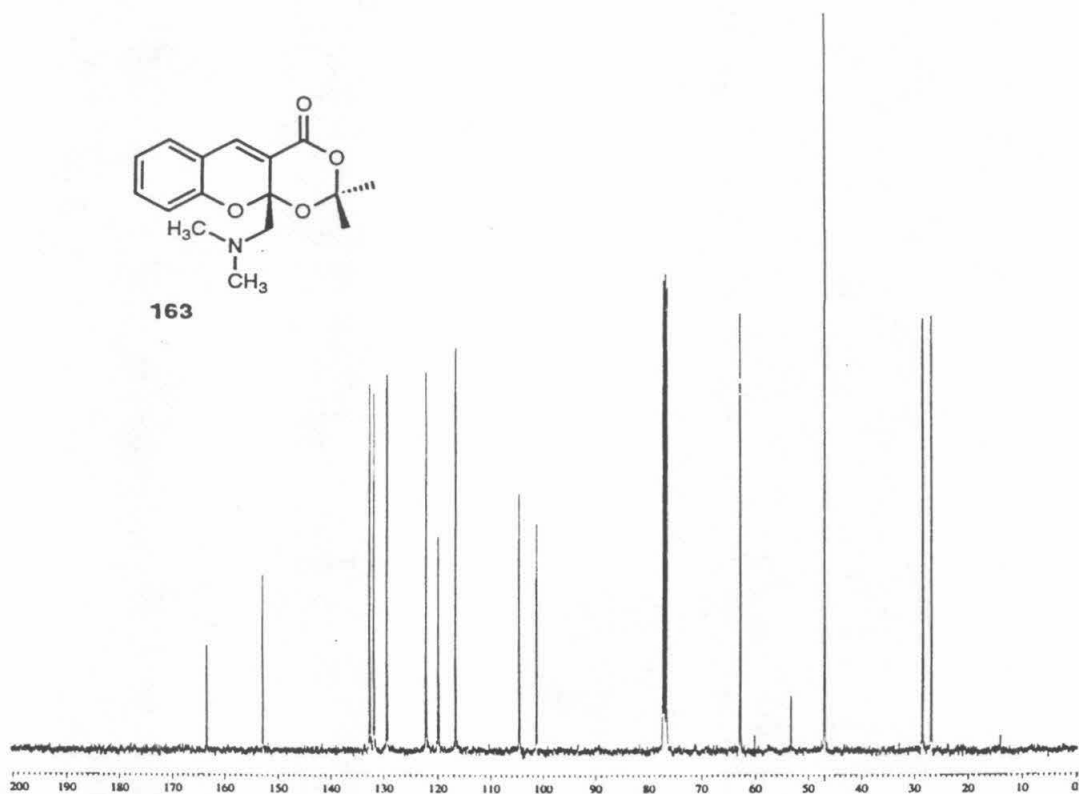
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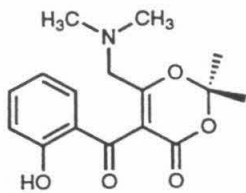




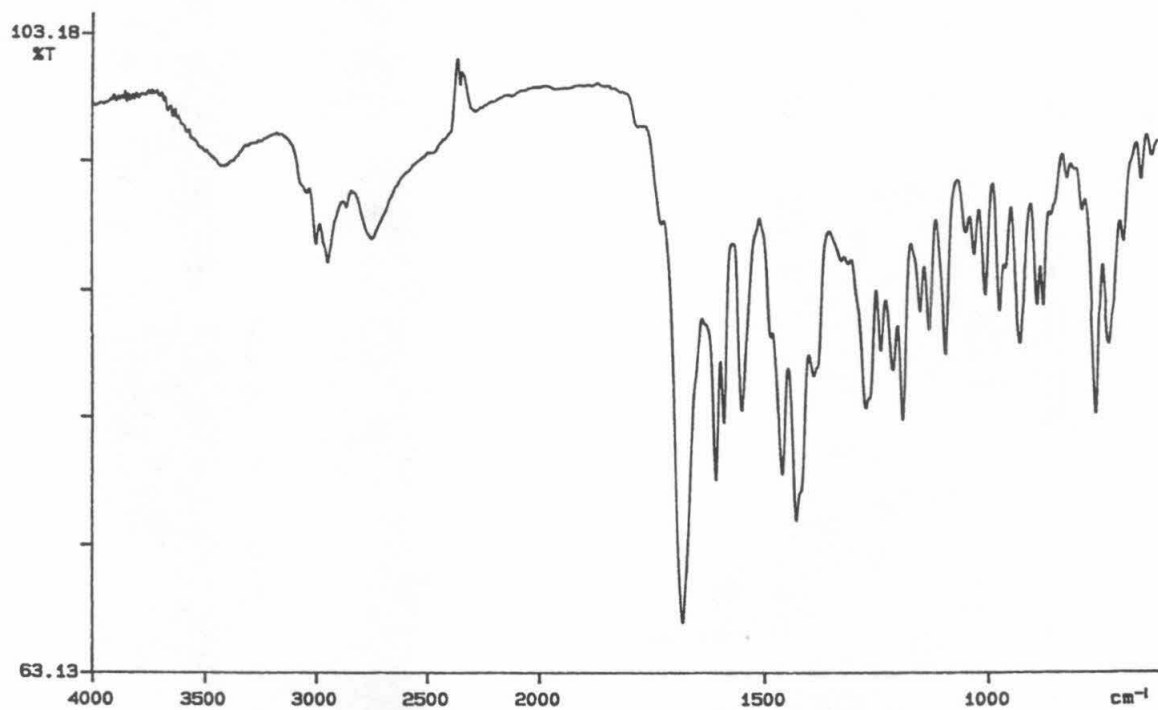
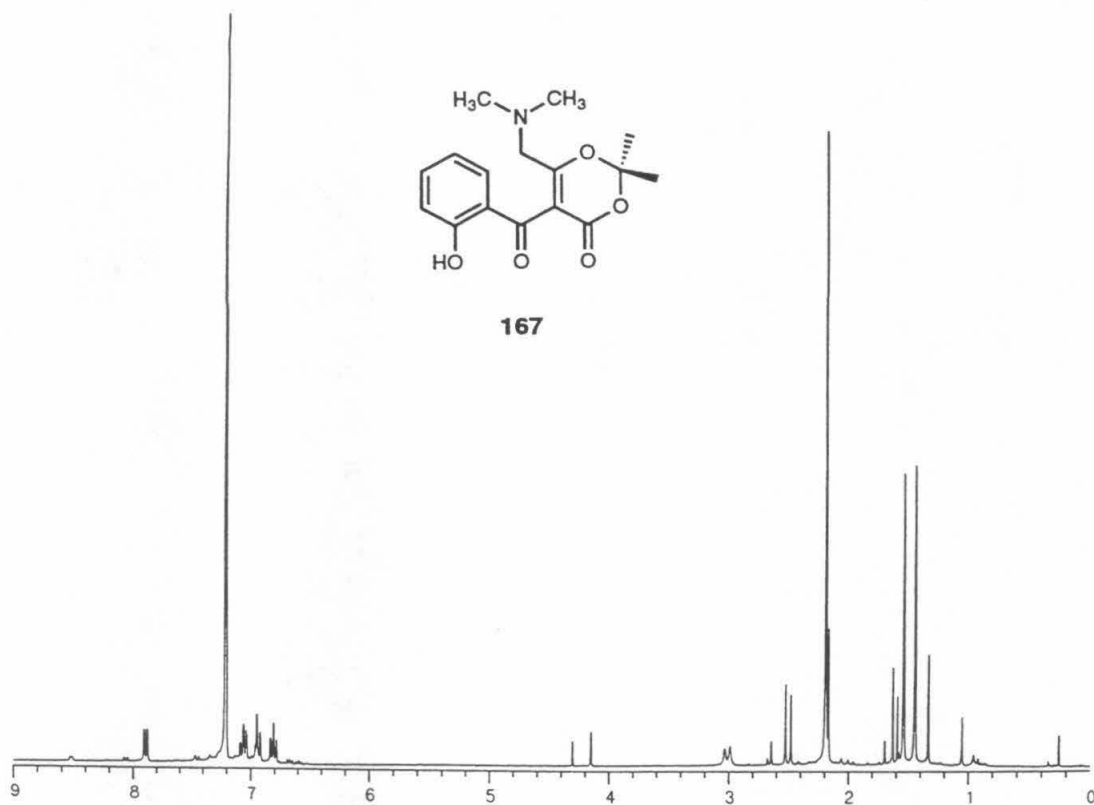
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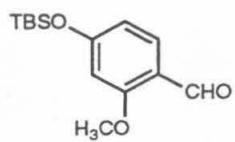


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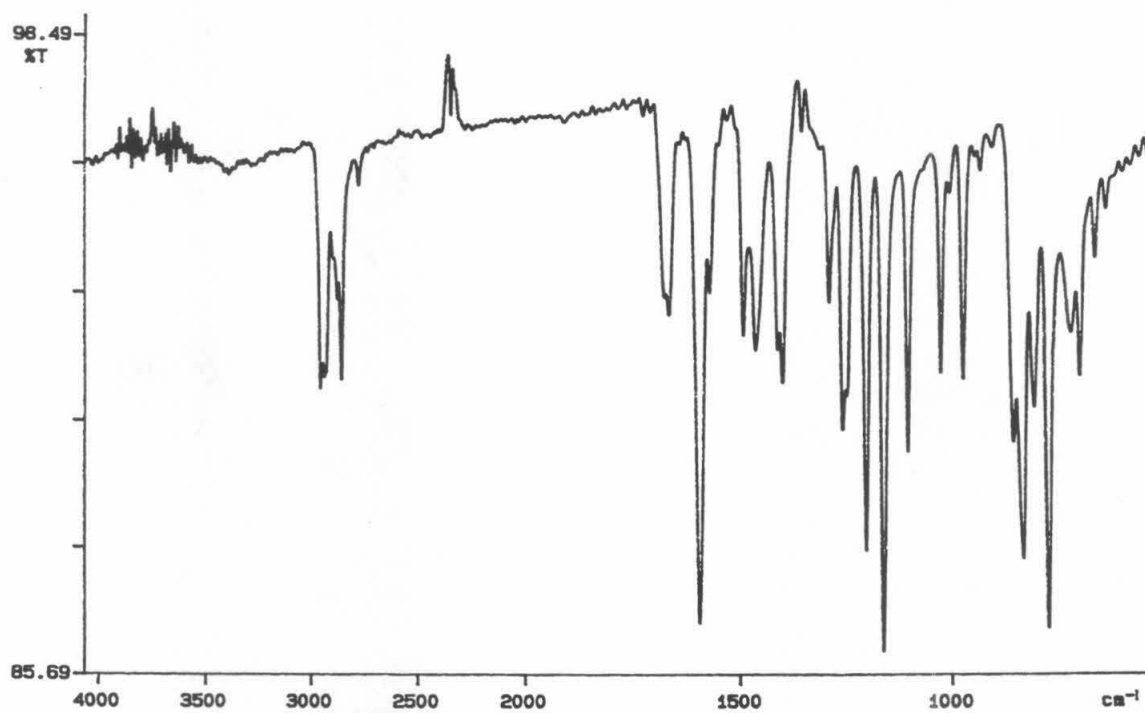
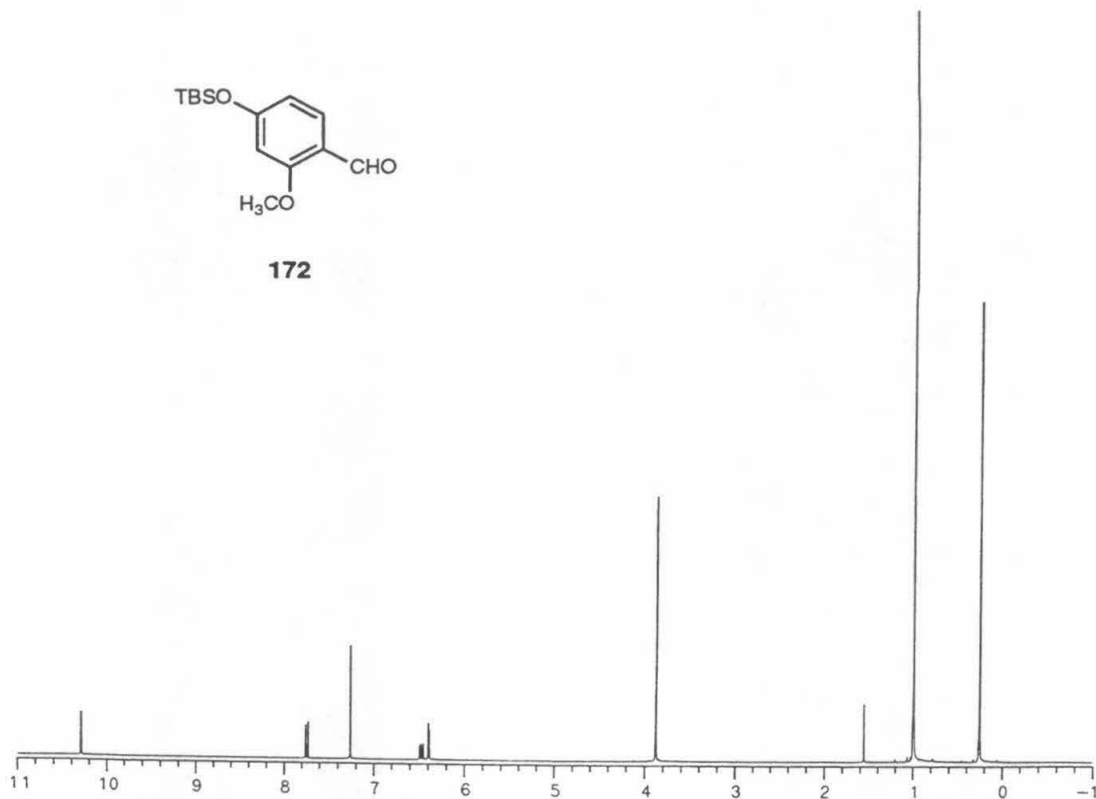


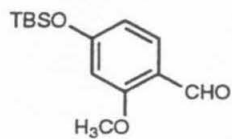
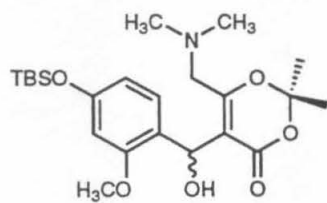
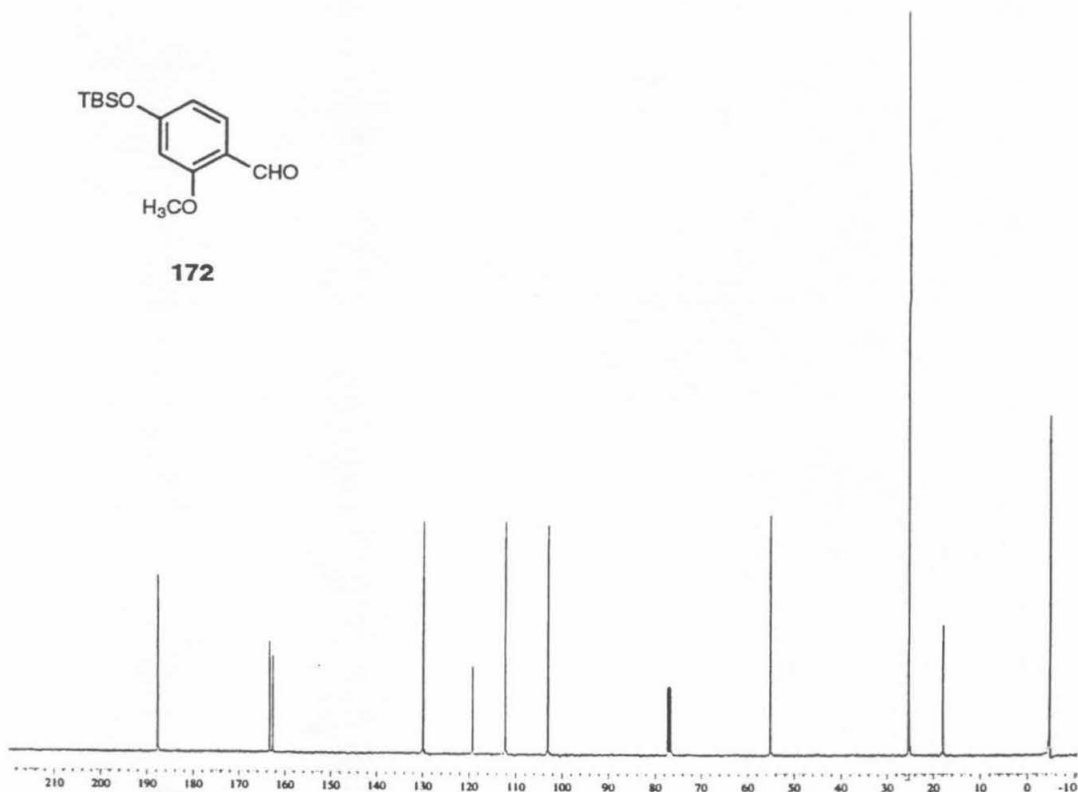
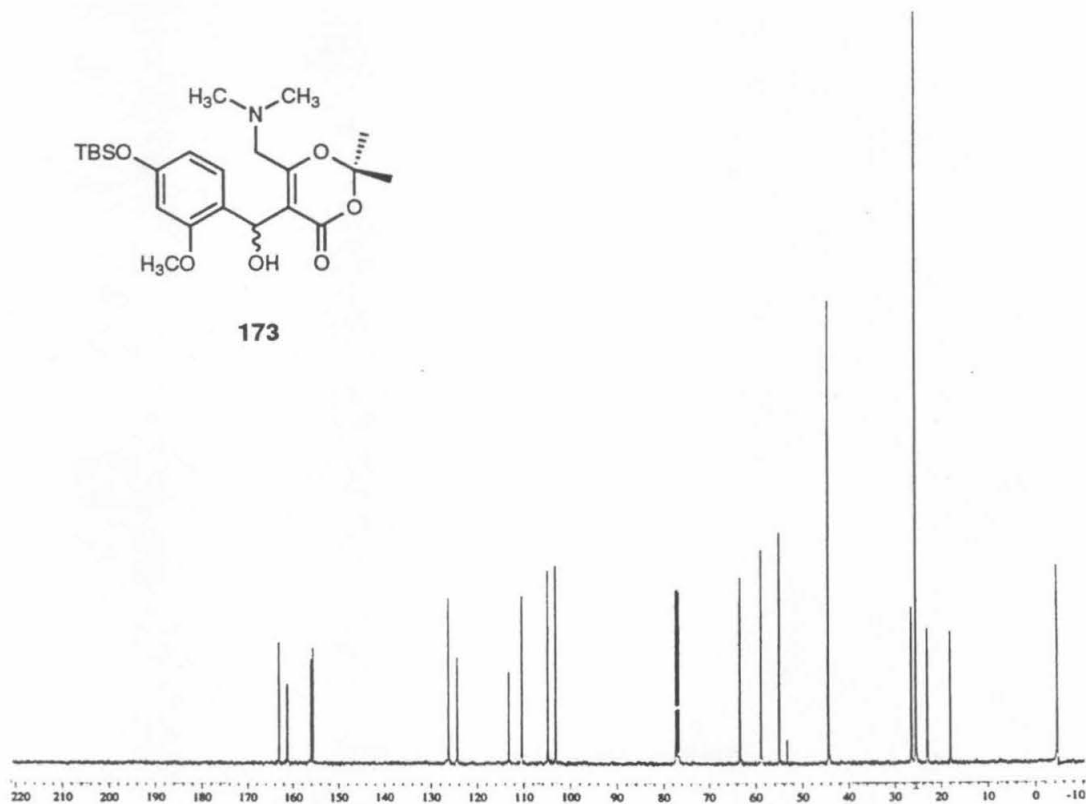
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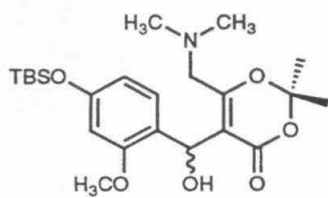




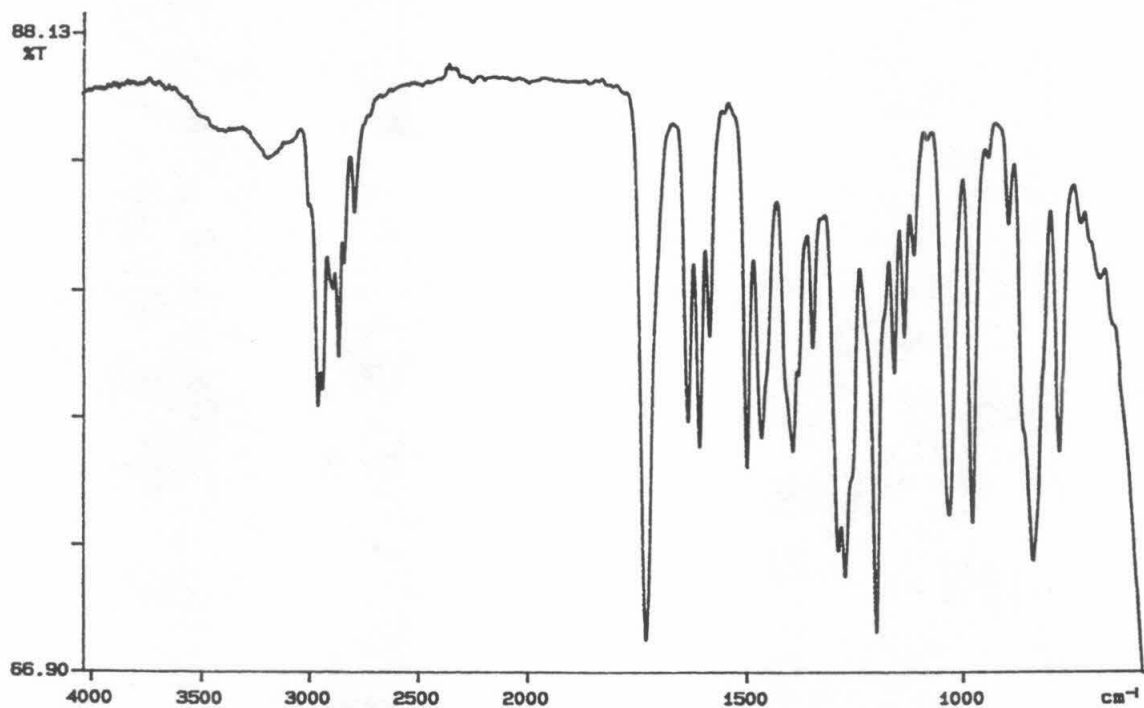
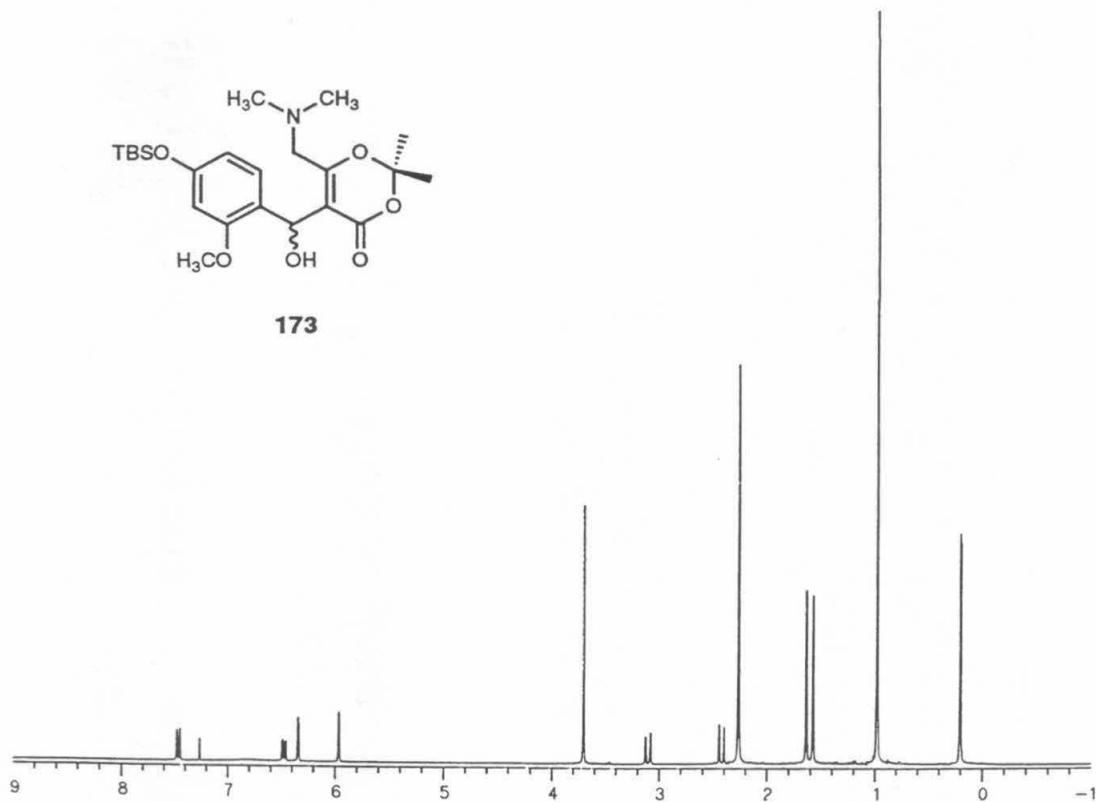
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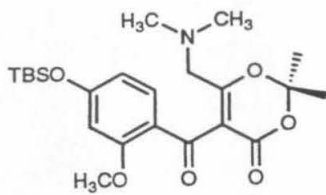


**172****173**

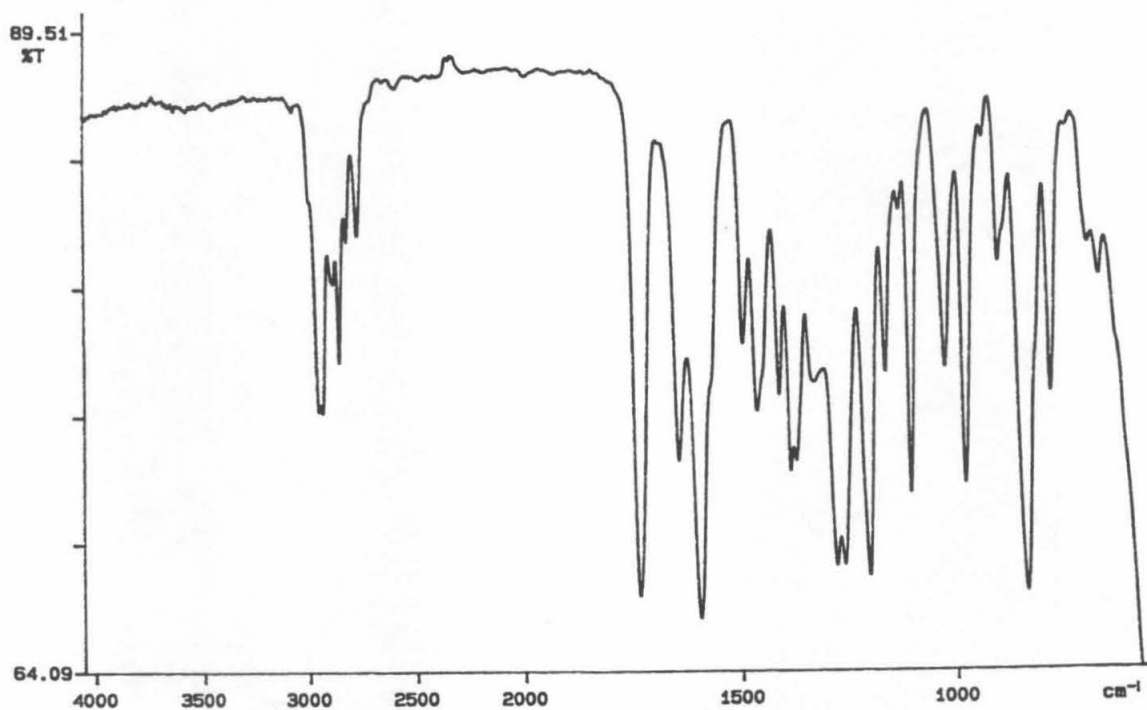
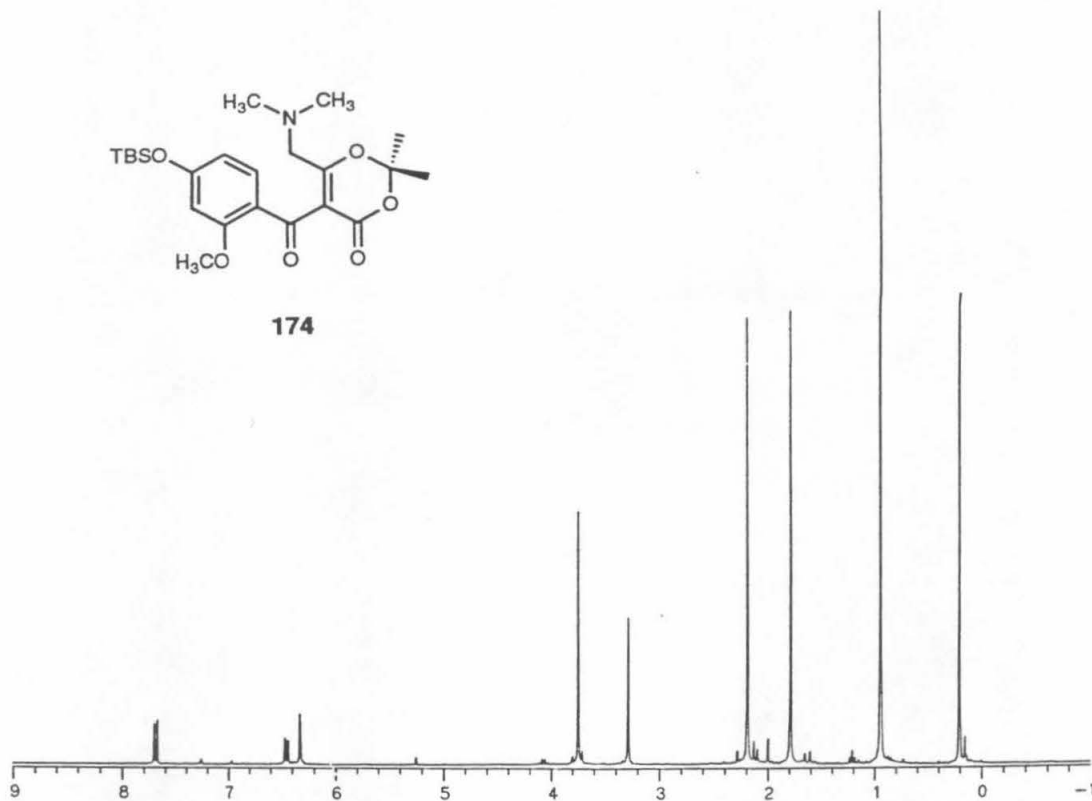


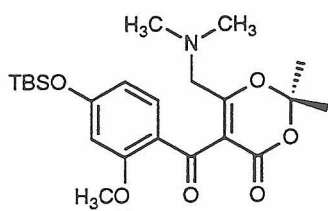
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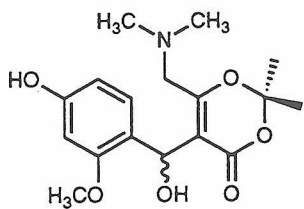
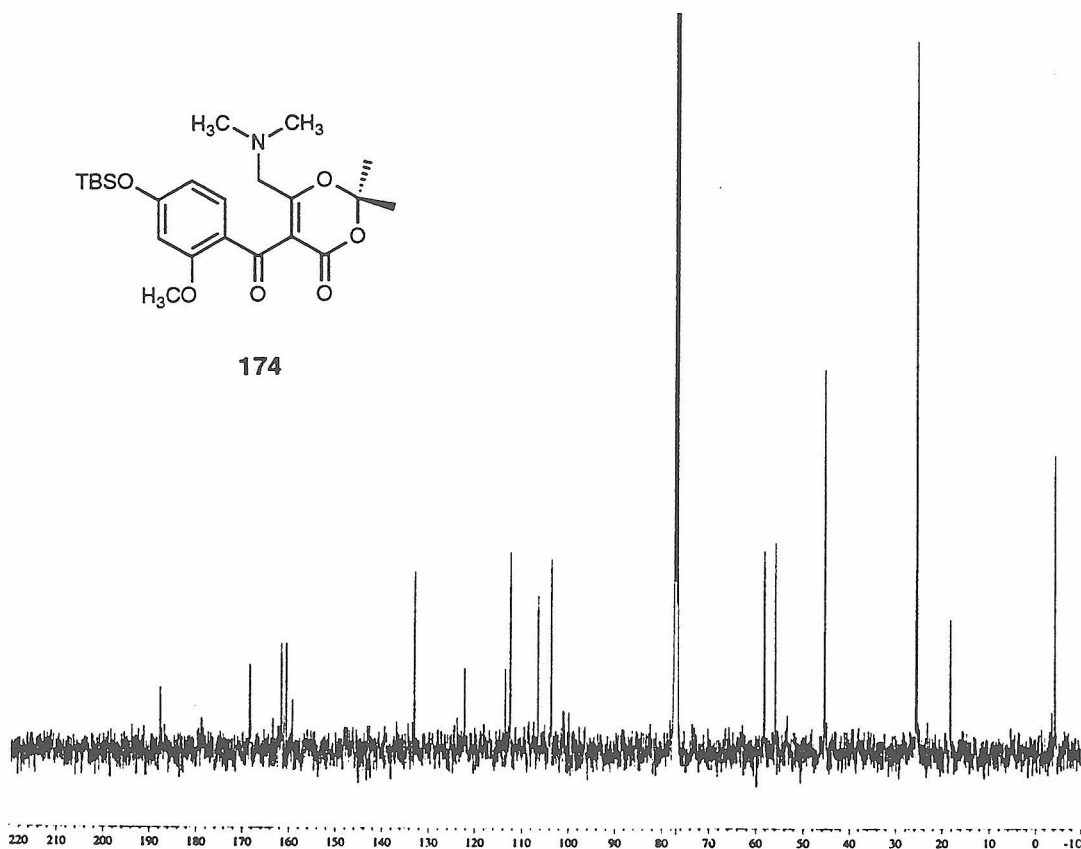


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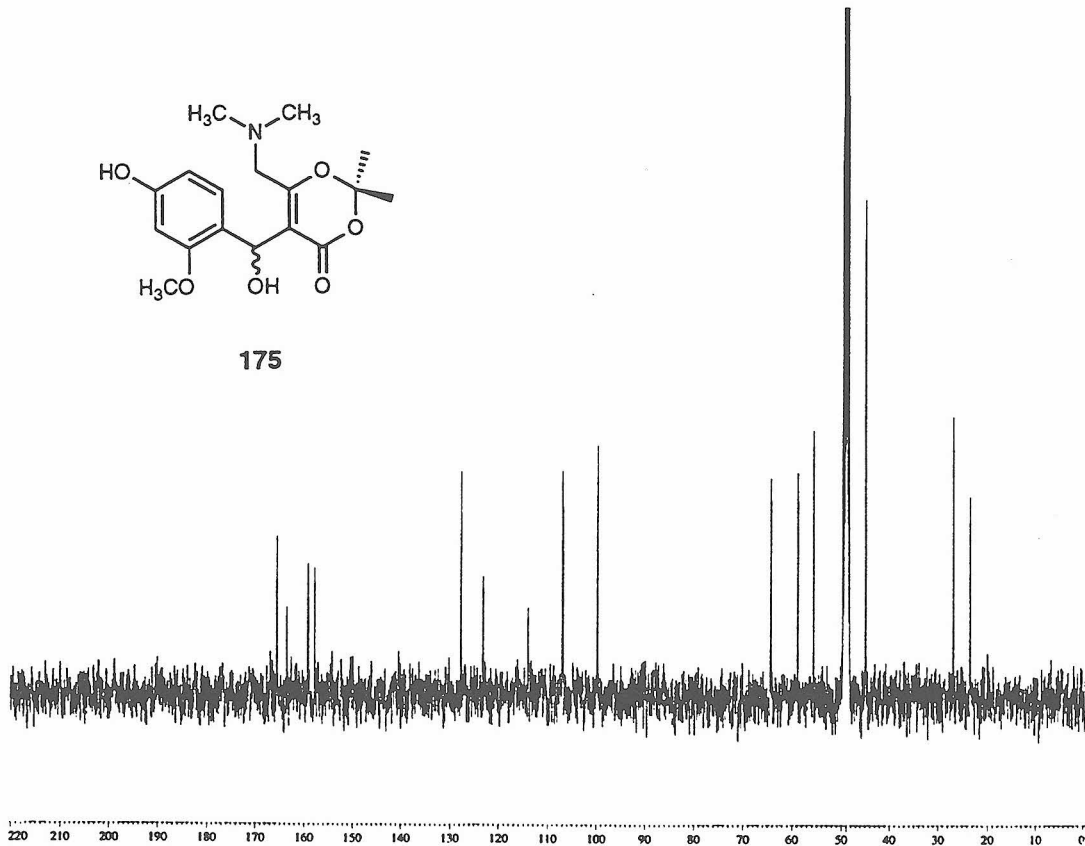




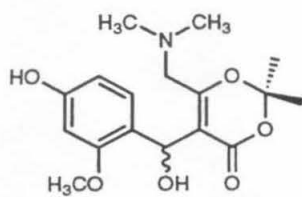
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